U82
RR

SURGERY
Gynecology & Obstetrics

WITH

INTERNATIONAL ABSTRACTS OF SURGERY

UNIV OF CALIFORNIA
LOS ANGELES
MAR 5 1958
BIOMEDICAL LIBRARY

March, 1958

VOLUME 106 • NUMBER 3

NEW

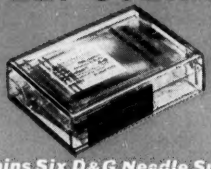
Get this compact, convenient D & G EMERGENCY SUTURE PACK for bag or office

REVOLUTIONARY! SIMPLE! STERILE!

JUST STRIP OPEN...SLIP OUT STERILE INNER ENVELOPE

- No jars or solutions
- No clumsy glass tubes to break
- No nicked sutures or adhering glass splinters
- Sterile needle suture ready for use in seconds

Order your D&G EMERGENCY SUTURE PACK from your Surgical Supply Dealer...or fill out and mail coupon direct to us.



Contains Six D&G Needle Sutures In Individual, Quick-Opening SURGILOPE SP* Sterile Strip Packs.

Compact, plastic snap-catch box—3½" x 2½" x ¾". Contains six sterile D & G Atraumatic® Needle Sutures: 3 Anacap® Silk, 4-0, ⅜ circle regular cutting needle; 3 Dermalon® Monofilament Nylon, 4-0, ⅜ circle inverted cutting needle. Each suture individually protected in quick-opening Surgilope SP Sterile Strip Pack.

*Trademark

CYANAMID

AMERICAN CYANAMID COMPANY
SURGICAL PRODUCTS DIVISION
DANBURY, CONNECTICUT

Producers of Davis & Geck Brand Sutures and Vim Brand Hypodermic Syringes and Needles. Distributed in Canada by: North American Cyanamid Ltd., Montreal 16, P. Q.

American Cyanamid Company, Surgical Products Division, Danbury, Conn.

Please send me_____ Emergency Suture Packs, at $4.00 each.
(quantity)

Bill me through my nearest SPD Dealer, or the SPD Dealer I have listed below.

_____ M.D.
(name)

_____
(address)

Surgical Supply Dealer _____
(name)

_____
(address)

SURGERY
Gynecology & Obstetrics
MARCH 1958
VOLUME 106
NUMBER 3

CARCINOMA OF THE COLON AND RECTUM

R. W. POSTLETHWAIT, M.D., F.A.C.S., J. E. ADAMSON, M.D., and DERYL HART, M.D., F.A.C.S., Durham, North Carolina

AN ANALYSIS of 1,023 patients with carcinoma of the colon or rectum seen at Duke Hospital during the 25 year period ending December 1955 is reported. We have previously reported on the 441 patients seen during the first 15 years of this period (26). In the last 10 years, an additional 582 patients with malignant tumors of the colon or rectum were seen. These two groups form a logical division for comparison of certain aspects of the study.

INCIDENCE

The rectum was the most frequent site, comprising 47.2 per cent of the 1,023 patients (Table I). The sigmoid was second with 19.5 per cent and the cecum third with 8.7 per cent. The sex incidence was almost equally divided: 49.5 per cent were males and 50.5 per cent females. Carcinoma of the rectum was slightly more frequent in men, whereas the occurrence of carcinoma of the sigmoid was higher in women. By age, the highest incidence was in the group whose ages were 61 to 70 years (Table II); 68.5 per cent of the patients were more than 50 years of age and 31.5 per cent were younger.

From the Department of Surgery, Duke University School of Medicine and the Veterans Administration Hospital, Durham, North Carolina.

HISTORY

Fifteen per cent of the patients had a family history of malignant tumor. Seventy patients, or 6.8 per cent, had an abdominal operation after the onset of symptoms of the malignant tumor and before coming to this hospital. These operations consisted of: colostomy in 20 cases, ileostomy in 2, resection of the neoplasm in 24, exploratory laparotomy in 16, and appendectomy in 8. During the same period, after the onset of symptoms, 9 per cent of the patients in the first 15 year group had hemorrhoidectomy or injection of hemorrhoids, whereas in the second 10 year period, this decreased to 4 per cent. Although not tabulated, it was noted that each year, an increasing proportion of patients with carcinoma of the rectum came to the hospital having had a positive histologic diagnosis.

The average duration of symptoms in months showed no noteworthy changes.

In the 1946 to 1955 group, 12 of the 582 patients had asymptomatic tumors. Seven of these were found at operation for other causes. Three patients were found to have

TABLE I.—SITE, SEX, AND RACE OF 1,023 PATIENTS

	Total		Male		Female		White		Negro	
Site*	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
R	483	47.2	249	24.3	234	22.9	369	36.1	114	11.1
RS	63	6.2	29	2.8	34	3.4	55	5.4	8	.8
S	199	19.5	80	7.8	119	11.7	167	16.4	32	3.1
DC	43	4.2	19	1.9	24	2.3	39	3.8	4	.4
SF	22	2.1	16	1.5	6	.6	17	1.6	5	.5
TC	42	4.1	18	1.7	24	2.3	34	3.3	8	.8
HF	31	3.0	17	1.6	14	1.4	27	2.6	4	.4
AC	51	5.0	32	3.1	19	1.9	45	4.4	6	.6
C	89	8.7	48	4.7	41	4.0	74	7.3	15	1.4
Total	1,023	100.0	508	49.5	515	50.5	827	80.8	196	19.2

*In this and subsequent tables, all abbreviations for site of lesions are: R, rectum; RS, rectosigmoid; S, sigmoid; DC, descending colon; SF splenic flexure; TC, transverse colon; HF, hepatic flexure; AC, ascending colon; C, cecum.

TABLE II.—AGE DISTRIBUTION

	Years							
Site	10-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
R	3	14	50	71	126	158	51	10
RS		2	11	12	16	16	6	
S		8	17	38	52	57	25	2
DC	1	1	1	10	7	7	4	
SF		1	3	8	6	10	5	1
TC		2	3	10	8	10	7	2
HF		2	3	8	6	10	2	
AC	1	1	5	6	15	16	7	
C	1	3	6	21	27	18	12	1
Total	6	34	99	184	263	302	119	16
Per cent	.6	3.3	9.6	18.0	25.8	29.6	11.6	1.5

TABLE III.—PERCENTAGE INCIDENCE AS FIRST SYMPTOM AND TOTAL INCIDENCE OF EACH SYMPTOM

	Right colon 171 patients		Left colon 306 patients		Rectum and RS 546 patients	
	First	Total	First	Total	First	Total
Abdominal pain	55.8	74.0	34.7	64.8	6.4	25.6
Melena	4.7	31.6	22.2	53.6	34.6	80.6
Constipation	2.8	17.6	15.4	35.4	20.9	39.4
Diarrhea	7.1	17.0	6.9	17.0	12.8	27.3
Weakness	13.5	28.8	2.3	10.2	1.3	8.1
Mass	5.9	18.8	1.6	5.9	—	.7
Anorexia	—	11.0	—	5.2	—	1.6
Nausea	—	18.2	.3	14.7	—	3.3
Vomiting	.5	16.5	—	13.4	—	2.0
Distension	.8	6.5	2.7	15.7	.7	4.6
Tenesmus	—	—	.3	5.9	2.2	21.6
Decreased caliber	—	—	1.3	8.2	.5	19.6
Mucus in stool	—	—	.6	9.8	.7	19.0
Alternate diarrhea and constipation	—	.8	1.6	5.5	1.1	4.4
Rectal fullness or pain	—	—	—	2.3	8.0	19.7
Urinary	—	—	—	—	.2	4.0
Acute obstruction	3.5	—	5.5	—	—	—
Other	.8	3.5	1.6	2.3	.2	3.1

carcinoma of the rectum, and 1 patient had carcinoma of the rectosigmoid found on routine physical examination during investigation of complaints not related to the large bowel. One patient, under treatment for prostatitis, had an asymptomatic carcinoma of the splenic flexure seen by barium enema.

For the analysis of symptoms, the 1,023 patients were divided into three groups: (1) right colon group included those with malignant lesions in the cecum, ascending colon, hepatic flexure, or proximal portion of the transverse colon; (2) the left colon group included the remainder of the transverse colon, splenic flexure, descending colon, and sigmoid; (3) the rectal group included rectum or rectosigmoid. The incidence of each symptom is shown in Table III, and the most frequent symptoms in each group are compared in Figure 1.

In both the right and left colon groups, abdominal pain was the most frequent symptom. No detailed analysis was made regarding location, severity, or character of radiation of the pain because of the many variations of this manifestation, as the pain would be dependent in the individual patient on the site of the lesion, degree of obstruction, presence of infection, and possibly other factors. In the right colon group, the first symptom was pain in 55.8 per cent of patients and occurred at some time during the illness in 74.0 per cent. For the left colon group these percentages were 34.7 and 64.8 per cent and for the rectal group 6.4 and 25.6 per cent respectively.

The second most frequent symptom in the right colon group was melena, but the second most common first symptom was weakness which was noted by 13.5 per cent of these patients. In 28.8 per cent weakness was a prominent symptom during the illness. This was a manifestation of the severe anemia which developed slowly without other outstanding symptoms. Not infrequently a history of having received several transfusions was obtained, the cause of the anemia having been obscure in the absence of symptoms other than weakness. In the right colon group, 5.9 per cent of the patients felt an abdominal mass before other symptoms were experienced, and a total of 18.8 per cent of these patients felt a mass before coming to the hospital. As the first symptom, diarrhea was noted by 7.1 per cent of the patients whereas constipation accounted for only 2.8 per cent of the original complaints. The total incidence of these symptoms, however, was almost the same, as diarrhea occurred in 17.0 per cent and constipation in 17.6 per cent.

Abdominal pain, melena, and constipation made up a triad accounting for the symptoms in the majority of patients with carcinoma of the left colon. Pain was the first symptom in 34.7 per cent and was eventually noted in 64.8 per cent, melena was the first symptom in 22.2 per cent and occurred in 53.6 per cent, and constipation

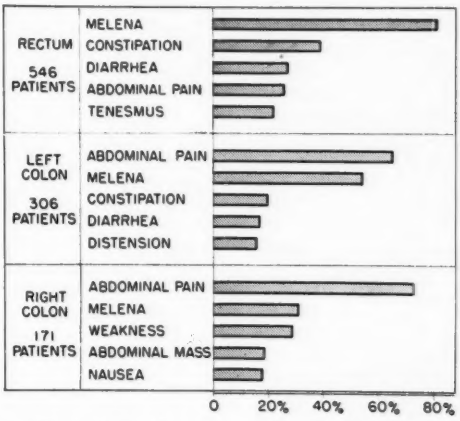


FIG. 1. Comparison of 5 most frequent symptoms.

was the first symptom in 15.4 per cent and occurred in 35.4 per cent. Diarrhea was present in 17.0 per cent, exactly the same incidence as noted in the right colon group. Nausea, vomiting, and abdominal distention were infrequently early symptoms but were noted at some time by approximately one-sixth of the patients. Acute intestinal obstruction as the first symptom developed in 5.5 per cent of the left colon group and in 3.5 per cent of the right colon group.

In those patients with a rectal tumor, the presence of blood in the stool was the first symptom in 34.6 per cent and occurred at some time during the illness in 80.6 per cent. Constipation and diarrhea were also frequent symptoms, initially occurring in 20.9 and 12.8 per cent of the patients, and developing eventually in 39.4 and 27.3 per cent. Symptoms which might be expected to be due to the anatomic site of the lesion were: tenesmus in 21.6 per cent, rectal pain or fullness in 19.7 per cent, decreased caliber of the stool in 19.6 per cent, and mucus in the stool in 19.0 per cent.

In the 1931 to 1945 series, the average weight loss was 25.6 pounds in those patients for whom the weight loss was known. The 1946 to 1955 group showed no noteworthy change in this respect, but of interest were those patients who had no weight

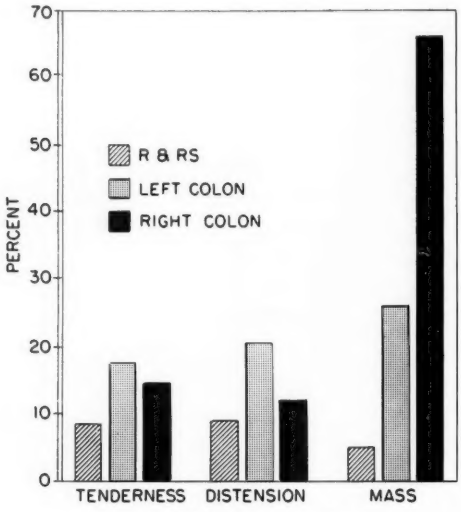


FIG. 2. Abdominal examination.

loss. Among the patients who made a definite statement regarding weight, 22 per cent of those with a lesion of the right colon, 34 per cent of those with a lesion of the left colon, and 31 per cent of those with a lesion of the rectum had no weight loss.

PHYSICAL EXAMINATION

The major findings on examination of the abdomen are shown in Figure 2. A palpable abdominal mass was the most frequent sign of importance. In the 1931 to 1945 series, a mass was felt in 69 per cent of the patients with right colon lesions and in 62 per cent of the same group in the 1946 to 1955 series. For those who had a lesion in the left colon, 35 per cent in the early series and 17 per cent in the more recent series had a palpable mass. If abdominal distention is used as the index of intestinal obstruction, then this complication was considerably less frequent in the 1946 to 1955 series as the percentage of patients with distention decreased from 15 to 9 per cent in the right colon group and from 28 to 13 per cent in those with carcinoma in the left colon. The degree of tenderness was variable and was usually not severe. Signs of peritoneal irritation were infrequent.

Of the rectal lesions, 94 per cent were palpable by rectal examination and the remainder were seen by proctoscopy. Carcinoma of the rectosigmoid was palpable by rectal examination in 32 per cent of these patients, and was not palpable but was visible by proctoscopy in 38 per cent. No proctoscopic examination was recorded in 25 per cent of those with a rectosigmoid lesion and 5 per cent had this examination but the tumor was not visualized.

The most frequent complicating and concurrent diseases were: hypertensive vascular disease in 103 patients, cardiac disease with decreased reserve in 99, and diabetes in 14. Marked obesity was noted in 29 patients. Generalized arteriosclerosis and benign prostatic hypertrophy were frequently noted but were not tabulated.

LABORATORY EXAMINATIONS

Hemoglobin determination, white blood cell count, blood serology, and urinalysis were carried out on all patients. Most of the patients in the 1931 to 1945 series and all of those in the 1946 to 1955 series had a chest roentgenogram made. Special examinations were performed as indicated. The degree of anemia as represented by the hemoglobin determinations was more severe in patients with a malignant tumor of the right colon (Fig. 3).

Thirty-five per cent of the patients in the right colon group had less than 9 grams of hemoglobin compared to 14 per cent for the left colon group, and 10 per cent for those with rectal lesions.

Barium enema examination was not performed in every patient. This procedure was occasionally omitted in those with lesions which had caused complete obstruction. The radiologist was always advised of the clinical impression in order to avoid the complication of barium impaction proximal to the tumor. Barium enema was usually carried out in those with nonobstructing rectal lesions in order to rule out polyps or a sec-

ond malignant tumor in the colon. In the 214 recorded barium enema examinations for left colon lesions, 147 showed a change either diagnostic or highly suggestive of malignancy, 64 had an appreciable degree of obstruction, and 3 examinations were negative. Of 148 barium enema examinations for right colon lesions, 122 showed a defect in the colon and 26 demonstrated obstruction.

MULTIPLE CARCINOMAS

In the 582 patients comprising the 1946 to 1955 series, 30 patients with multiple primary carcinomas were found, which is an incidence of 5.2 per cent. Five patients had 2 carcinomas of the colon (patients with multiple polyposis were excluded). In 1 patient, a carcinoma of the sigmoid and a second carcinoma in the transverse colon were removed at the same operation. A patient with chronic ulcerative colitis at the time of colectomy had a carcinoma in the cecum and in the descending colon. In 1 patient a carcinoma of the cecum was removed, and 6 months later a second operation was performed for removal of carcinoma of the transverse colon. Another patient had resection of malignant tumors of the sigmoid and transverse colon with an interval of 3 years, and the fifth patient had cecal and sigmoid lesions with an 8 year interval.

Twenty-two patients had a carcinoma of the colon or rectum and another carcinoma as follows: of the breast in 5; cervix, 4; stomach, 2; uterus, 2; pancreas, 2; lymphosarcoma, 2; testicle, 1; skin, 1; prostate, 1; fibrosarcoma, 1; and Hodgkin's disease, 1. Three patients had 3 primary cancers, appearing in the following order: breast, colon, and alveolar ridge; breast, colon, and skin; stomach, colon, and prostate.

DISPOSITION OF PATIENTS

Of the 1,023 patients, 105 were not admitted to the hospital. Forty-one refused to be admitted, and so far as could be determined, had no definitive treatment. Twenty-seven went elsewhere for treatment. Eighteen were obviously inoperable and were sent home for terminal care. Seven were given palliative irradiation, and 12 were seen for consultation only.

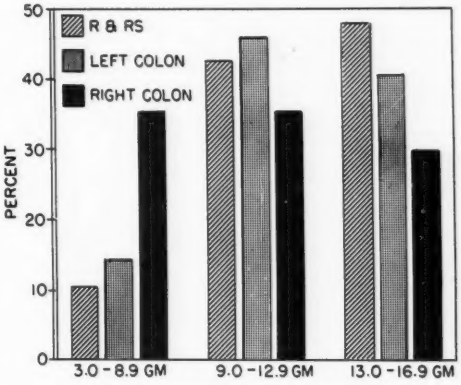


FIG. 3. Hemoglobin determinations.

One hundred and twenty-six patients were admitted to the hospital but had no colon operation. Forty-nine patients of this latter group clinically had an inoperable tumor, most often because of a nodular liver or a fixed rectal lesion with frozen pelvis. Nine patients were inoperable for reasons other than the malignant tumor, usually severe cardiovascular disease. Forty patients refused operation, 12 were admitted for palliative x-ray therapy, and 16 were not operated upon for other reasons. The latter included those who died of other disease and those who had previously been treated elsewhere and had a recurrence.

Seven hundred and ninety-two patients had an operation directly related to the colon lesion.

PREOPERATIVE CARE

After the diagnosis was established, measures were directed toward the treatment of: intestinal obstruction; nutritional, fluid, and electrolyte alterations; and concurrent disease.

The attainment and maintenance of an empty bowel before and after operations has been considered the most important single factor in the recovery of these patients. A low residue, soft or liquid diet, laxatives,

TABLE IV.—OPERATIVE PROCEDURES IN 792 PATIENTS

	Right colon	*Left colon*	*Rectum or RS*
Palliative			
Exploration only	10	20	14
Colostomy	0	35	89
By-pass	21	6	0
Resection	13	34	28
Miscellaneous	3	0	0
Preliminary			
Colostomy	0	19	11
Cecostomy	0	19	5
Definitive			
Resection and anastomosis	92	128	15
Exteriorization	0	38	2
Combined resection	0	10	196
Miscellaneous	1	5	23

and enemas were routinely employed. A Miller-Abbott or Cantor tube for gastrointestinal tract suction was used shortly before operation routinely, and was employed when indicated for incomplete obstruction for a variable period preoperatively. Because of complete obstruction, colostomy or cecostomy was necessary in 54 patients as a preliminary procedure before a definitive or palliative operation could be carried out. Cecostomy was performed in 24 of these patients; colostomy in the remaining 30.

Drugs were given to most patients for decreasing the bacterial count of the large bowel. In the earlier series of cases, sulfasuxidine was used most often but in the later group streptomycin, neomycin, or terramycin was administered. Other antibiotic agents were given as indicated. Fluid and electrolyte imbalance were ascertained by history, examination, and laboratory determinations and were corrected by appropriate therapy. Transfusions were administered in the treatment of anemia. Vitamins were routinely given, particularly ascorbic acid. The cardiac, respiratory, and renal systems were thoroughly investigated and any indicated treatment was given.

OPERATIONS

The various surgical procedures performed on the 792 patients are shown in Table IV. Metastases or invasion were present in 273 patients so that operation could not be done with any hope of cure. Exploratory laparotomy only was done in this group in 16 per cent, a colostomy in 45 per cent, and a by-pass procedure in 10 per cent. The latter was usually ileocolostomy and occasionally colocolostomy. A palliative resection was performed in 27 per cent. The conditions preventing definitive resection were as follows: metastases to the liver 92, invasion of the pelvic or abdominal wall 82, abdominal carcinomatosis 44, peritoneal implants 39, invasion of the urinary bladder 36, remote lymph node involvement 24, and miscellaneous 10. The total number of causes preventing definitive resection was greater than the total number of patients as more than one condition was found in a number of patients.

The definitive operations were those in which the surgeon thought that the tumor had been completely removed and reasonable hope of cure was justified. Resections for lesions of the right colon have remained essentially unchanged throughout the series. End-to-end anastomosis was performed more frequently in recent years than end-to-side ileotransverse colostomy. In the early years, some type of exteriorization procedure was usually carried out for tumors of the left colon. Resection and closed anastomosis then gradually became the procedure of choice and for the past several years, resection with open anastomosis has become practically routine. A gradual trend toward more extensive resection for carcinoma of the left colon also became evident in the later part of the series. The one stage combined abdominoperineal resection of Miles remained the procedure of choice for the rectal and rectosigmoid lesions. More frequent employment of anterior resection for the rectosigmoid and upper rectal tumors was noted in the more recent years. Sphincter preserving procedures such as the pull-through operation were seldom performed.

RESECTABILITY

Resectable lesions were those in which hope of cure could be held and did not include the palliative resections. Resectability in a

TABLE V.—PERCENTAGE DEFINITIVE RESECTABILITY

	R	*RS*	*S*	*DC*	*SF*	*TC*	*HF*	*AC*	*C*
Total patients									
1931–1945	34	41	49	60	62	62	59	43	45
1946–1955	50	53	62	65	57	61	71	71	51
Patients operated upon									
1931–1945	54	54	56	63	62	62	77	83	55
1946–1955	71	66	68	71	66	64	71	74	60

series may be determined on the basis of the total number of patients seen, of the patients admitted, or of the patients subjected to operation. Determination on the basis of the total patients seen should be the most reliable index, but this percentage would be distorted by those who refused operation or went elsewhere for treatment and by those who came to the hospital because of recurrence after resection elsewhere. The resectability percentage in our series was determined on the basis of the total number of patients seen and also on the basis of the total number treated surgically (Table V). By either calculation, resectability was increased in the 1946 to 1955 series in the rectum, rectosigmoid, sigmoid, and cecum, which were the sites in which the majority of tumors occurred. Considering the entire group of 1,023 patients, operability was 77 per cent and resectability 50 per cent. For the 1931 to 1945 series, operability was 72 per cent and resectability 41 per cent; for 1946 to 1955, 82 per cent and 56 per cent respectively. This represents a significant increase in operability from 72 to 82 per cent; resectability from 41 to 56 per cent.

PATHOLOGY

All of the resected lesions and the inoperable tumors from which a biopsy was obtained were adenocarcinomas with 4 exceptions in the 1931 to 1945 series. These were 3 lymphosarcomas and 1 unclassified sarcoma. In the 1946 to 1955 series, tumors other than adenocarcinoma were omitted. The lesions were not graded or classified. The presence or absence of lymph node metastases was not noted on the pathologic report in a number of cases, and as many of the specimens had been destroyed, this omission could not be corrected. In those cases in which this information was available, the incidence of lymph node involvement was as follows: rectum and rectosigmoid, 43 per cent positive; left colon, 28 per cent positive; and right colon, 29 per cent positive.

POSTOPERATIVE COMPLICATIONS

The nonfatal complications in the 792 patients operated upon included 26 wound infections and 10 wound disruptions. Fifteen patients had ileus of more than the usual extent and 2 had intestinal obstruction requiring laparotomy. Four patients had peritonitis and 3 others a pelvic abscess. Thrombophlebitis was noted in 17 patients and pulmonary embolism in 4 patients. Ten had atelectasis or pneumonia, and parotitis occurred 3 times in the 1931 to 1945 series. Four patients had a persistent perineal urinary fistula. Urinary bladder disturbance and infection in minor degree were relatively frequent, although less so in the 1946 to 1955 series, and were not tabulated. Two patients had a cerebral vascular accident. Two severe transfusion reactions were recorded and 1 instance of homologous serum jaundice. One patient in the early series had a thyroid crisis but recovered. One patient had gangrene of the colostomy loop after a combined abdominoperineal resection and 2 who had sphincter preserving procedures were complicated by gangrene of the proximal large bowel segment. In 1 case of carcinoma of the descending colon, resection and primary anastomosis were performed despite a large firm fecal mass proximally. The anastomosis broke down but drainage resulted in eventual healing.

OPERATIVE MORTALITY

All deaths which occurred during operation or the postoperative period of hos-

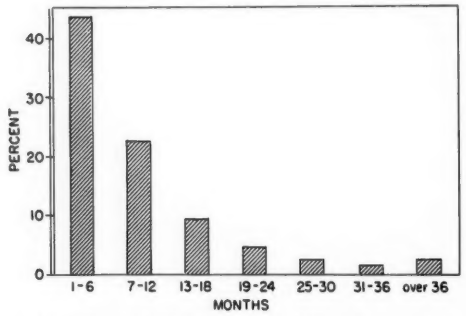


FIG. 4. Survival time in months, 273 exploratory or palliative operations; 10 per cent died in the hospital, 1.8 per cent were lost, 2.2 per cent are living.

pitalization are included in these statistics. These deaths are summarized in Tables VI, VII, and VIII. The decrease in operative mortality in recent years was obvious. In the 1931 to 1945 series, 20 of the 57 deaths were due to peritonitis; in the 1946 to 1955 group, 6 of the 21 deaths were caused by peritonitis. This represented a decrease of deaths due to peritonitis from approximately 35 to 29 per cent of the total deaths, although over-all mortality rate decreased from approximately 18 to 4 per cent.

RESULTS

The results following palliative operations in 273 patients are shown in Figure 4 in which the bar graph represents those known to be dead after discharge from the hospital. Only 2.2 per cent were known to be living and these patients had survived from 6 to 36 months. The longest survival was 80 months after operation. The mortality in the first year was 76.6 per cent in the 235 patients who survived hospitalization and for whom the time of death was known. From the tabulation noted, few patients with nonresectable lesions can be expected to live for more than 1 year. Palliative operations in many cases, however, contributed greatly to the comfort of the patient, and palliative procedures, particularly resections, were therefore carried out whenever feasible.

TABLE VI.—POSTOPERATIVE MORTALITY BY 5 YEAR PERIODS

	Palliative		*Preliminary*		*Definitive*	
	No. operations	*Deaths, per cent*	*No. operations*	*Deaths, per cent*	*No. operations*	*Deaths, per cent*
1931-1935	21	14.3	3	33.3	22	31.8
1936-1940	50	16.0	11	27.3	51	15.7
1941-1945	55	16.4	12	33.3	110	12.7
1946-1950	73	5.5	16	6.3	179	4.5
1951-1955	74	4.1	13	0	148	3.4

The results of the definitive resections are shown in Table IX. The 5 year survival percentage was determined first, on the basis of the total number of patients seen during the 20 year period, and secondly, on the basis of the total number of definitive resections performed in each group. In determining the percentage of total resections, postoperative deaths were excluded and patients lost to follow-up counted as dead. The 5 year survival of the 519 patients seen with rectal or rectosigmoid carcinoma was 14.5 per cent, and the 5 year survival of those who had definitive resection was 49.7 per cent. For 211 patients with carcinoma of the left colon, survival for the entire group was 25.6 per cent and for those resected 50.0 per cent. In the right colon group of 133 patients, 27.1 per cent survived 5 years or 53.7 per cent of those resected.

DISCUSSION

The distribution by site in this series is similar to others reported. In most series, males have outnumbered females, whereas, the reverse was true in our group by a narrow margin. The race incidence in this series cannot be considered representative, as most patients were referred and, therefore, a certain degree of selectivity must have occurred. At this hospital, however, approximately 1 patient in every 4 admitted is a negro and 1 patient with malignant large bowel tumor in every 5 was a negro, which suggests more nearly equal race incidence than that found by others. The distribution by age also resembles other series; over half of the patients are in the 50 to 70 year age group.

Familial polyposis has been well established as predisposing to cancer of the colon

TABLE VII.—POSTOPERATIVE DEATHS FOR PERIOD 1946 TO 1955 ONLY

No.	*Year*	*Site*	*Operation*	*Cause*	*P.O. day*	*Autopsy*
			PALLIATIVE OPERATIONS			
1	1950	R	Colostomy	Peritonitis	2	Yes
2	1949	S	Resection	Shock	1	Yes
3	1955	DC	By-pass	Cardiac failure	5	No
4	1949	TC	Exploration	Carcinomatosis	7	Yes
5	1946	AC	Cecostomy	Carcinomatosis	51	No
6	1955	AC	Resection	Peritonitis	70	Yes
7	1955	C	By-pass	Pulmonary edema	3	No
			PRELIMINARY OPERATION			
8	1947	S	Colostomy	Cardiac failure	16	No

The deaths in the 1931-1945 series were tabulated as above in the previous report.

TABLE VIII.—POSTOPERATIVE DEATHS FOR THE PERIOD 1946 TO 1955 ONLY

No.	*Year*	*Site*	*Operation*	*Cause*	*P.O. day*	*Autopsy*
			DEFINITIVE OPERATIONS			
1	1946	R	Abd. per. resection	Peritonitis	1	Yes
2	1946	R	Abd. per. resection	Hemorrhage	0	Yes
3	1947	R	Abd. per. resection	Peritonitis	5	Yes
4	1949	R	Abd. per. resection	Pneumonia	9	No
5	1954	R	Pull-through	Perforation esophagus	5	Yes
6	1948	RS	Abd. per. resection	Pulmonary embolus	11	Yes
7	1953	S	Abd. per. resection	Peritonitis	19	Yes
8	1954	S	Resection and anastomosis	Cerebral vascular accident	3	Yes
9	1947	SF	Exteriorize	Hemorrhage	0	Yes
10	1948	TC	Resection and anastomosis	Peritonitis	87	Yes
11	1953	TC	Right colon resection	Cardiac arrest, cerebral damage	4	No
12	1950	AC	Right colon resection	Cerebral vascular accident	4	No
13	1955	AC	Right colon resection	Thrombosis superior mesenteric artery	7	Yes

TABLE IX.—RESULTS OF DEFINITIVE RESECTIONS 1931 TO 1950

					5 year survivors			
Site	*Total patients*	*Total resections*	*Postop. deaths*	*Lost*	*Now living*	*Now dead*	*Per cent total patients*	*Per cent total resections*
R	470	151	16	3	45	20	13.8	48.1
RS	49	20	4	1	6	4	20.4	62.5
S	127	74	7	0	28	9	29.1	55.2
DC	34	22	2	2	9	2	32.4	55.0
SF	18	10	1	1	2	0	11.1	22.2
TC	32	14	2	0	1	3	12.5	33.3
HF	25	16	0	3	6	4	40.0	62.5
AC	37	20	1	2	9	2	29.7	57.9
C	71	36	4	6	11	4	21.1	46.9

and was recently reviewed by McBurney and Sanders. In our series 1.2 per cent had familial polyposis. Adenomatous polyps of the colon are precursors of malignancy and should be removed. The remaining colon should be inspected through separate colotomy incisions with visualization through a sterile sigmoidoscope, as in Bacon's series, multiple polyps were present in 33 per cent of patients; Helwig noted 42 per cent multiple polyps and Thompson and Pinck found 25 per cent. Richards and Woolf investigated a large family descended from a male progenitor who died of melanoma. Four of his 24 children had cancer of the colon, and half of the 62 patients of the third generation examined had adenomatous polyps, suggesting the possibility of an inherited tendency in the formation of solitary polyps. The percentage of adenomatous polyps which become malignant or the percentage of carcinoma arising from these polyps is difficult to determine but is thought to be high.

The frequency of carcinoma of the colon in patients with chronic ulcerative colitis

varies in reported series. Felsen and Wolarsky, for example, followed-up 855 patients with chronic ulcerative colitis and none had developed carcinoma of the colon to the time of the report. The consensus, however, appears to be that these patients are subject to an increased risk of developing large bowel cancer. This risk is probably about 5 per cent after having ulcerative colitis for 5 years, with each year increasing the chances of developing a cancer. In addition, several other aspects of this association appear to be well established: carcinoma develops at a younger age, is highly malignant, is frequently multicentric, and ileostomy or partial colectomy do not prevent development of carcinoma in the remaining large bowel.

The duration of symptoms in the two groups in this series showed disappointingly little change. The information available was inadequate to assign culpability accurately, but the patient was usually responsible for the delay. In the last 5 years, many more patients came to the hospital with the diagnosis of carcinoma of the colon or rectum already established by biopsy or radiographic study.

The symptomatology in carcinoma of the colon and rectum has been well established. With lesions of the right colon, a small, but definite group had an abdominal mass as the only or the main complaint. A second group with carcinoma of the right colon noted weakness as the predominant feature of their illness and this was usually related to severe anemia, a manifestation noted by others. Delay in recognition of the primary right colon lesion occurred when the physician assumed the anemia was nutritional in origin and treated the patient accordingly. Over one-third of this series of patients had less than 9 grams of hemoglobin with right colon lesions, compared to 14 per cent and 10 per cent for the left colon and rectum groups.

Rapidly developing, complete obstruction after few or no previous symptoms was present in an appreciable number of patients; over 5 per cent of the left colon group. Gius described this acute obstruction as due to a compensatory hypertrophy with increased work capacity of the proximal bowel musculature as the tumor develops, then sudden decompensation when a certain degree of obstruction is reached.

Weight loss has been given frequently as one of the prominent symptoms of malignancy. One third of our patients had no weight loss and this symptom, although of interest, should not be necessary to arouse suspicion of malignancy.

In the physical examination of these patients, all of the rectal lesions could be felt or could be seen by proctoscopy, and about a fourth of the sigmoid lesions could be visualized. Two-thirds of the right colon lesions had a palpable mass and approximately a fourth of the left colon tumors. Therefore, approximately 75 per cent of the patients had a lesion which could be felt or seen and a reasonably accurate diagnosis established by the simple maneuvers of abdominal palpation, and rectal and sigmoidoscopic examination.

Barium enema examination was carried out in most of these patients and was remarkably accurate. In the acutely obstructed patient, a small barium enema was carefully given when necessary to establish the diagnosis. Patients with nonobstructing rectal and rectosigmoid tumors were given a barium enema to rule out polyps or a second carcinoma of the colon.

The incidence of multiple adenomatous polyps would suggest the probability of multiple independent carcinomas of the colon. Ginzburg and Dreiling have recently reviewed this problem and reported a group of 25 such cases found in approximately 700 large bowel resections for cancer. Others have published similar reports with an incidence up to 4.6 per cent. The incidence in this series was just over 1 per cent. The possibility of multiple malignant neoplasms is always sufficient to require appropriate steps before and during operation to rule out a second tumor and to necessitate proper

follow-up to diagnose early a later cancer.

The manner of the preoperative preparation of these patients was determined by a number of factors but the presence or absence of obstruction was undoubtedly the most important. MacFee and others have justifiably emphasized the importance of recognition and treatment of intestinal obstruction in their discussions of the management of carcinoma of the colon. The patient with an unobstructed colon usually presented little difficulty in preoperative care with the administration of the proper diet, laxatives, and enemas. A slight to moderate degree of obstruction frequently responded to the same measures. Complete or nearly complete obstruction necessitated other treatment. Obstructed lesions of the right side of the colon usually responded to suction via one of the long tubes. With complete obstruction in the left side of the colon, little could be gained from prolonged delay and dependence on tube suction, as only about 10 per cent will escape emergency surgery. In our series, cecostomy or transverse colostomy was usually necessary; sigmoid colostomy was performed occasionally for rectal lesions.

The proper use of cecostomy versus colostomy has been the subject of some controversy and Maynard and Turell have recently defined the indications for each. The patient with complete obstruction is dangerously ill and a lifesaving procedure performed with minimal general and local trauma is needed. Cecostomy under local anesthesia can be carried out with little insult to the patient and will provide adequate decompression for the closed loop obstruction. After cecostomy, however, considerable difficulty may be encountered in obtaining adequate cleansing of the distal bowel unless partial relief of the obstruction follows. Colostomy may be done with almost as little trauma if carefully performed, produces the necessary decompression, and later allows irrigation and emptying of the distal segment. Defunctionalization of the distal colon occurs only by separation of the two colostomy loops, but partial defunctionalization will follow proper care and dressing of the loop colostomy. An additional advantage of colostomy, which is usually performed through a larger incision than cecostomy, is a very gentle exploration which may, at times, be done to avoid errors in diagnosis. Such exploration, however, may increase the possibility of peritonitis and should not be carried out routinely. Later closure of the colostomy will be necessary whereas the cecostomy usually closes spontaneously. Careful evaluation of the individual patient, with particular attention to general physical status, degree and site of obstruction, and nature of the fecal content of the colon proximal to the lesion should determine the preliminary procedure to be carried out.

The contributions of Poth (27, 28) and of Cohn and Longacre (5, 6) have emphasized the value of intestinal antisepsis before large bowel surgery. At this institution, Anlyan, Hart, Georgiade, and Poston have studied this problem and concluded that neomycin is currently the drug of choice for this purpose. The necessity for investigation and treatment of concurrent disease, nutritional deficiency, anemia, and fluid and electrolyte alterations requires no elaboration.

The value of palliative resection has been emphasized by Modlin and Walker and Stearns and Binkley. Colostomy or a by-pass procedure such as ileotransverse colostomy suffice to avoid the effects of obstruction, but offer little else as palliation. As palliative resection does not increase morbidity and mortality in properly selected cases this should be done whenever feasible. The obstruction is relieved or avoided, the source of blood loss and the site of infection removed, and invasion with resultant intractable pain possibly prevented. Palliative resection has been more frequently performed at Duke Hospital in recent years. In our latter series of cases, 59 patients who had palliative colostomy or by-pass procedure lived an average of 6.9 months; the longest survival was 24 months.

Palliative resection in 65 patients resulted in an average survival of 13.6 months; the longest was 47 months, and 9 patients lived for more than 2 years. Even these gains in terms of time did not equal the benefits in nutrition and in comfort.

The definitive resections were those performed in which the surgeon believed that all of the tumor had been removed and hope of cure could be held. At this hospital, as in most others, a gradual trend toward more extensive resections has been accompanied by more frequent attempts to extend resectability, however justifiable this may be. Resections for lesions in the right side of the colon have changed mainly in the use of open end-to-end anastomosis of ileum to transverse colon rather than closed end-to-side restoration. The left colon lesions were usually removed by an exteriorization procedure early in the series. Later, resection with closed anastomosis was employed and now open anastomosis is almost routinely used. Proximal cecostomy or colostomy is now seldom done at the time of resection.

In the lower sigmoid, rectosigmoid, and rectum, the one-stage combined abdominoperineal resection of Miles has been carried out in most patients. Sphincter-saving pull-through procedures were done in a few patients, but the complications were so frequent that this procedure has been abandoned almost completely. The indications for anterior resection have gradually been extended and this procedure has been employed with greater frequency in recent years. Recently reported survival studies would appear to justify this change. The careful studies concerning invasion and lymph node metastases by Miles, Dukes and Bussey, Coller, Kay, and MacIntyre, Gilchrist and David (13, 14), Glover and Waugh, Grinnell, Astler and Coller, Black and Waugh, Quer, Dahlin, and Mayo, and others have contributed greatly to the establishment of a sound basis for selection of the proper procedure for rectal and rectosigmoid lesions. A number of investigators have pointed out the less satisfactory results in low rectal lesions, lateral spread usually being the factor implicated. The procedure of choice is combined abdominoperineal resection for low rectal lesions. The high rectal lesions are treated by anterior resection by most of the surgeons in this hospital although occasionally combined resection is still performed. The midrectal lesions (6 to 15 cm.) have usually been treated by combined resection, but a definite increase in the frequency of anterior resection is apparent. The margin of normal rectum which remains below the lesion should be the determining factor. If a margin of 5 to 8 centimeters cannot be obtained, lymphatic drainage along the middle hemorrhoidal group at the levator ani or downward intramural spread may compromise the operation and combined resection is more clearly indicated. The means of decreasing possible spread described by Cole (7, 8), Fisher and Turnbull, and others involving early vessel ligature and proximal and distal occlusion of the bowel lumen to prevent venous tumor emboli and intraluminal spread to the suture line are important and have recently been utilized.

The decrease in postoperative mortality has been gratifying and is similar to other recently reported series. In the past 5 years, no deaths occurred after preliminary decompressing operations, whereas, a mortality of 30 per cent was found in the 1931 to 1945 group. This reflects, in part, the improved treatment of intestinal obstruction and its accompanying alterations. The progressive decrease in mortality for definitive procedures from 32 per cent in the first part of the series to 3.4 per cent in the past 5 years has been encouraging. In the 1931 to 1945 series, peritonitis was the cause of death in 35 per cent of those who died after operation and this figure decreased only to 29 per cent for the 1946 to 1955 series. It is apparent that in spite of the over-all improvement in mortality and the availability of chemotherapeutic and antibiotic agents, infection remains a problem. The aid from these latter agents cannot be considered a substitute for an accurate anastomosis on a

decompressed bowel with an adequate blood supply, a fact emphasized by Lockwood.

The 5 year survivals in our series were about average when compared with other reports. Considerable difficulty occurs in accurate comparison with those reported groups in which palliative resections are included or postoperative deaths and patients not followed are excluded. Welch and Giddings have discussed the various methods of reporting 5 year survivals and suggest that 2 figures should be given: (1) based on all cases seen and (2) based on curative resections, minus postoperative deaths, with all lost to follow-up counted as dead. If the survival percentages are based on all patients seen, whether or not admitted, clinical diagnosis will have to be accepted in some cases, and the statistics will also be affected by those who have been operated upon elsewhere, who refuse admission, and similar cases. The attitude of the surgeon in accepting or rejecting poor risk patients, and in attempting to extend curative resection will also influence these percentages. The suggestion of Welch and Giddings, however, appears well founded and our 5 year survivals are recorded by the two methods noted. Included in the 5 year survivors are patients now dead. This is fair, particularly in this age group, because of the considerable number of patients who die of causes other than carcinoma. The sources of information as to the cause of death are not always reliable, but in our series a number died of other lesions.

In most of the anatomic sites, the 5 year survival was about the same as other reported series, as already noted. The very low survival rates for the splenic flexure and transverse colon groups were very disappointing, and further extension of the limits of resection may be of doubtful value. The survival in the hepatic flexure group was unusual in that this site usually shows the lowest survival rate. The exact reason for this was not clear as the extent of resection, usually to midtranverse colon, was the same as reported by others.

SUMMARY

A group of 1,023 cases of carcinoma of the colon and rectum has been analyzed. About 75 per cent occurred in the rectal and sigmoid segments. The sex incidence was nearly equal, 19 per cent of the patients were negro and 55 per cent were in the 50 to 70 year age group. The predominant symptoms were abdominal pain, change in bowel habit, or change in stool. Diagnosis was seldom difficult. For the entire group, operability was 77 per cent and resectability 50 per cent. Postoperative mortality has gradually decreased and, during the last 5 years of the 25 year period, was 3.4 per cent for definitive resections. The 5 year survival after resection was 49.7 per cent for rectal, 50.0 per cent for left colon, and 53.7 per cent for right colon cases.

REFERENCES

1. Anlyan, W. G., Hart, D., Georgiade, N. E., and Poston, M. A. Intestinal antisepsis with oxytetracycline (terramycin) and neomycin. Arch. Surg., 1954, 68: 28-32.
2. Astler, V. B., and Coller, F. A. The prognostic significance of direct extension of carcinoma of the colon and rectum. Ann. Surg., 1954, 139: 846-852.
3. Bacon, H. E., and Peale, A. R. Appraisal of adenomatous polyps of the colon; their histopathology and surgical management. Ann. Surg., 1956, 144: 9-18.
4. Black, W. A., and Waugh, J. M. The intramural extension of carcinoma of the descending colon, sigmoid, and rectosigmoid. Surg. Gyn. Obst., 1948, 87: 457-464.
5. Cohn, I., Jr., and Longacre, A. B. Neomycin-nystatin for preoperative preparation of the colon. Am. Surgeon, 1956, 22: 301-307.
6. Idem. Tetracycline (achromycin)-neomycin for preoperative colon preparation. Arch. Surg., 1956, 72: 371-376.
7. Cole, W. H. Recurrence in carcinoma of the colon and proximal rectum following resection for carcinoma. Arch. Surg., 1952, 65: 264-270.
8. Idem. Precautions in the spread of carcinoma of colon and rectum. Ann. Surg., 1954, 140: 135-136.
9. Coller, F. A., Kay, E. B., and MacIntyre, R. S. Regional lymphatic metastases of carcinoma of the rectum. Surgery, 1940, 8: 294-311.
10. Dukes, C. E., and Bussey, H. J. R. Venous spread in rectal cancer. Proc. Roy. Soc. M., Lond., 1941, 34: 571-573.
11. Felsen, J., and Wolarsky, W. Chronic ulcerative colitis. Arch. Int. M., 1949, 84: 293-304.
12. Fisher, E. R., and Turnbull, R. B., Jr. The cytologic demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma. Surg. Gyn. Obst., 1955, 100: 102-108.
13. Gilchrist, R. K., and David, V. C. Lymphatic spread of carcinoma of the rectum. Ann. Surg., 1938, 108: 621-642.

14. Idem. Prognosis in carcinoma of the bowel. Surg. Gyn. Obst., 1948, 86: 359-371.
15. Ginzburg, L., and Dreiling, D. A. Successive independent (metachronous) carcinomas of the colon. Ann. Surg., 1956, 143: 117-120.
16. Gius, J. A. Role of hypertrophy of muscularis in delayed onset of symptoms in cancer of colon. Surgery, 1948, 24: 221-230.
17. Glover, R. P., and Waugh, J. M. The retrograde lymphatic spread of carcinoma of the "rectosigmoid region"; its influence on surgical procedures. Surg. Gyn. Obst., 1946, 82: 434-448.
18. Grinnell, R. S. Distal intramural spread of carcinoma of the rectum and rectosigmoid. Surg. Gyn. Obst., 1954, 99: 421-430.
19. Helwig, E. B. The evolution of adenomas of the large intestine and their relation to carcinoma. Surg. Gyn. Obst., 1947, 84: 36-49.
20. Lockwood, J. Letter to the Editor. Ann. Surg., 1950, 132: 319-320.
21. McBurney, R. P., and Sanders, R. L. Familial polyposis of colon. Am. Surgeon, 1956, 22: 583-594.
22. MacFee, W. F. The management of carcinoma in the several parts of the colon. Ann. Surg., 1947, 126: 125-139.
23. Maynard, A. D. L., and Turell, R. Acute left colon obstruction with special reference to cecostomy versus transversostomy. Surg. Gyn. Obst., 1955, 100: 667-674.
24. Miles, W. E. The pathology of the spread of cancer of the rectum and its bearing upon the surgery of the cancerous rectum. Surg. Gyn. Obst., 1931, 52: 350-359.
25. Modlin, J., and Walker, H. S. J. Palliative resections in cancer of the colon and rectum. Cancer, 1949, 2: 767-776.
26. Postlethwait, R. W. Malignant tumors of the colon and rectum. Ann. Surg., 1949, 129: 34-46.
27. Poth, E. J., Fromm, S. M., Martin, R. G., and Hsiang, C. M. Neomycin, an adjunct in abdominal surgery. South. M. J., 1951, 44: 226-231.
28. Poth, E. J., McNeil, J. P., Manhoff, L. J., Jr., King, W. B., and Sinclair, J. G. The healing of bowel as influenced by sulfasuxidine and streptomycin. Surg. Gyn. Obst., 1948, 86: 641-646.
29. Quer, E. A., Dahlin, D. C., and Mayo, C. W. Retrograde intramural spread of carcinoma of the rectum and rectosigmoid. Surg. Gyn. Obst., 1953, 96: 24-30.
30. Richards, R. C., and Woolf, C. Solitary polyps of the colon and rectum; a study of inherited tendency. Am. Surgeon, 1956, 22: 287-294.
31. Stearns, M. W., Jr., and Binkley, G. E. Palliative surgery for cancer of the rectum and colon. Cancer, 1954, 7: 1016-1019.
32. Thompson, J. E., and Pinck, R. L. Adenomatous polyps of the large bowel; their significance to the surgeon. Am. Surgeon, 1956, 22: 964-974.
33. Welch, C. E., and Giddings, W. P. Carcinoma of the colon and rectum. N. England J. M., 1951, 244: 859-867.

RESPIRATORY AND CARDIOVASCULAR PHENOMENA ASSOCIATED WITH PULMONARY EMBOLISM

RICHARD K. McEVOY, M.D., R. ALLAN HARDER, M.D., and
W. ANDREW DALE, M.D., F.A.C.S., Rochester, New York

PULMONARY EMBOLISM remains a dangerous and all too frequent occurrence following operation, trauma, or childbirth. The actual mechanisms of shock and death in clinical patients are still not completely understood. Numerous investigations are recorded in the literature with the development of two major hypotheses as to the causes of the lethal effects of pulmonary emboli, namely reflex effects and changes due simply to mechanical obstruction of the pulmonary vascular bed.

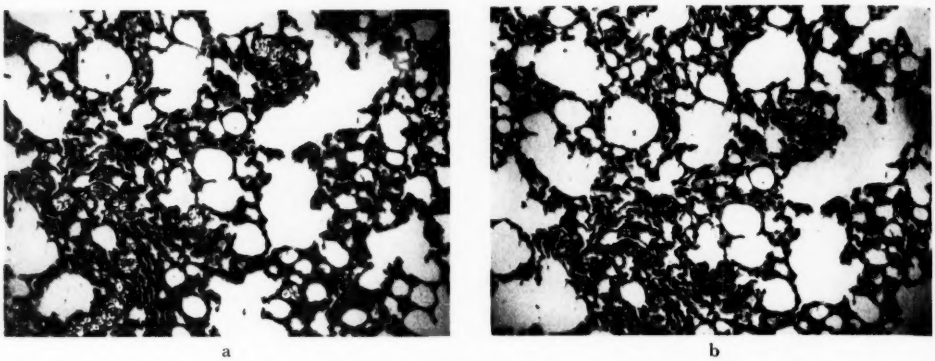
Earlier experimental and clinical investigations were summarized by DeTakats, Beck, and Fenn in 1939 and their investigations of a series of dogs were reported. Their study was based on crude mortality of pulmonary embolism in dogs with and without prophylaxis or treatment by drugs, and was interpreted as evidence that emboli caused reflex effects which could be modified by drugs or by autonomic nerve blocks. Holden, Shaw, Cameron, and Shea in 1949, Megibow, Katz, and Steinitz in 1942, Griffin and Essex in 1949, and Williams in 1956 reported studies indicating pulmonary arterial bed obstruction to be the essential physiologic lesion. On the other hand, there continues to be support for the reflex hypothesis such as the scholarly review of embolism by Whitteridge and the experimental results of Cate, Light, Daniel, and Edwards, who found changes in the pulmonary and systemic vascular pressures after localized pulmonary lobar embolization. More recently, Niden and Aviado in 1956 reported perfusion experiments whereby one lung of an anesthetized dog was perfused at a constant rate, while the lung still connected to the dog's heart was embolized with glass beads. They show a tracing of the perfused lobe's pressure which clearly increased following embolization of the other nonperfused lung. They interpret this as pulmonary vasoconstriction secondary to embolization.

The studies reported herein were designed to clarify further the role of reflexes or simple mechanical effects following pulmonary embolism, and are interpreted to indicate that under the conditions of the experiments in anesthetized dogs reflexes are of little importance when compared to the mechanical effects of pulmonary embolism.

METHODS

Dogs were anesthetized with intravenous nembutal, the initial dose being .026 gram per kilogram with small maintenance doses being given as infrequently as possible. Unsterile technique was used, as all experiments ended in sacrifice. Postmortem examination was usually limited to the thoracic viscera. Sections were routinely stained with hematoxylin and eosin, although phloxine-methylene blue staining was used for greater contrast when lead phosphate embolization had been done. Identification of starch emboli was facilitated by using a polarized light microscope. By this method, the starch granules stood out individually as bright discs with a "Maltese cross" shadow. Figure 1a is a photomicrograph under polarized light to demonstrate shining starch granules within pulmonary capillaries and arterioles.

From the Surgical Research Laboratory, Department of Surgery, University of Rochester School of Medicine and Dentistry, Rochester, New York.
Contract AF 41(657)-22, Air Research and Development Command, Randolph Field, Texas.



a b

FIG. 1. Comparison of photomicrographs of starch emboli, a, under polarized light, and, b, ordinary illumination.

Figure 1b shows the same section under ordinary light.

Emboli consisted either of commercial corn starch granules, small glass beads, or lead phosphate-agar gel. Commerical corn starch was weighed to form appropriate doses and suspended in 20 cubic centimeters of normal saline. Microscopic examination of this material showed that the particle size varied between 7 and 30 microns with most particles 15 to 20 microns. Glass beads were used in several sizes whose diameters averaged either 100 microns, 500 microns, or 1 millimeter. The lead phosphate-agar gel preparation was made as described by Schlesinger and used by Cate and associates. Doses of all these materials are described later. The suspended embolizing material was ordinarily passed through a polyethylene catheter threaded through the right jugular vein and lying just outside the right atrium. When the very large glass beads were used, a large catheter was placed directly into the main pulmonary artery at the time of thoracotomy, as described later, because these large beads obstructed the small polyethylene catheter and would not pass satisfactorily through the heart into the lung.

A bronchial divider as described by Dale and Rahn was placed through a left thoracotomy in certain experiments so that individual lung oxygen consumption determinations were possible. In brief, this bronchial divider consisted of a double plastic tube with one end cut long to allow it to be tied within the proximal portion of the left main bronchus. This lumen now carried air to the left lung, while the remaining lumen supplied the right lung, since the trachea was tied tightly about the entire divider at a higher level. When the two tubes were individually connected to 2 Collins respirometers, oxygen consumption records as well as tidal volume records for each lung could be obtained simultaneously.

Two and 3 lumen balloon catheters were "sailed" through the right heart into either the right or left main pulmonary artery by inflating the balloon and allowing the flow of blood through the heart to carry the catheter into the pulmonary artery. These catheters were patterned after those described by Lategola and Rahn. Figure 2 illustrates a triple lumen catheter the inner tube of which served for emboli injection into artery distal to the occluding balloon—which is served by the middle tube—while the outer tube served to measure the pulmonary artery pressure proximal to the occluding balloon. Certain experiments were performed with the pulmonary artery occluded by such an internal balloon. However, it was found that leakage of starch often occurred in a retrograde fashion

around this internal balloon, so a method for external pulmonary artery occlusion was developed as shown in Figure 3. Here, a small, thin-walled rubber tube was laid about the left pulmonary artery distal to the left upper lobar branch and enclosed in a collar of lucite. When air was pumped into this tubing, it expanded and compressed the pulmonary artery enclosed by it so that blood flow through the vessel ceased.

Perfusion of an isolated dog lung was performed after the method of Niden and Aviado. The left main pulmonary artery was isolated inside the pericardium and cannulated, or alternately, the long end of the left upper lobar artery was cannulated. A Sigmamotor pump whose rate of flow could be controlled was used to pump heparinized blood from another animal through this left lung of the anesthetized, but living, animal while the right lung continued to be supplied by the heart through the intact right pulmonary artery. The other end of the pump was connected via cannula to the femoral artery to withdraw blood in the same amount as that being perfused through the left lower lobe. This femoral artery blood was passed through the aorta of the donor dog and an equal volume simultaneously drawn from the donor dog's femoral vein to be passed through the pump into the perfused lobe. The lobe was, therefore, perfused with venous blood.

Sympathectomy was performed bilaterally through thoracotomy incisions so that the chain from its cervical portion to the eighth thoracic ganglion was completely excised. This method has been previously used in a series of animals reported by Stroud and Rahn and was an effective bilateral sympathectomy for pulmonary fibers in the dog.

Vagotomy was performed through bilateral cervical incisions by which both vagi in the neck were cut across.

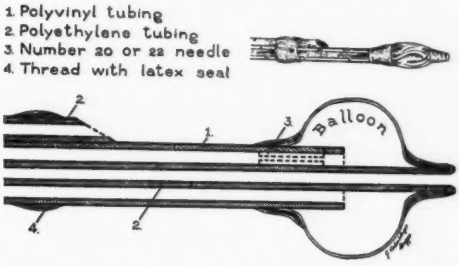


FIG. 2. Triple lumen catheter for transcardiac passage into pulmonary artery to allow pressure measurements both proximal and distal to occluding balloon and injection distal to balloon.

DISCUSSION OF RESULTS

Generalized Embolism

Generalized starch pulmonary embolism. By injection of starch (or other material) through a catheter lying in the superior vena cava just outside the right atrium, a general distribution of particles could be obtained in both lungs. Figure 4 shows typical data obtained when 1 gram of starch was injected at point 0 on the time line. Immediate pulmonary arterial pressure increase, aortic pressure decrease, and vena caval pressure increase occurred. The respiratory rate in the figure is too rapid for calculation, but other data show tachypnea under these conditions. A return toward control levels of pressure occurred very soon with return to approximately control levels at 20 minutes. Repetition of such doses of emboli produced the same response with, however, failure of return to control levels after further embolization so that a stepwise change occurred.

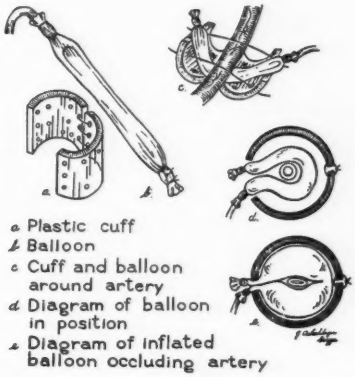

a Plastic cuff
b Balloon
c Cuff and balloon around artery
d Diagram of balloon in position
e Diagram of inflated balloon occluding artery

FIG. 3. Details of method of external tube compression of pulmonary artery.

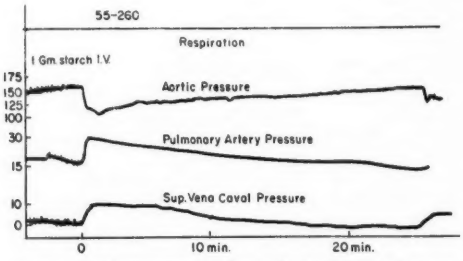


FIG. 4. Typical response of anesthetized dog to 1 gram starch embolism. Pressure in millimeters of mercury. Embolism occurred at 0 on time scale.

This observation is illustrated by Figure 6 (discussed later).

Figure 5 illustrates typical data obtained when generalized embolism was studied for 3 hours and shows the tendency to return toward control values over a long period. Such nonlethal doses of starch were well compensated by the dog. It seems likely that this compensation is associated with lessened pulmonary arterial resistance and may be due to release of vasoconstrictor tone or to vasodilatation. The compensatory phase then would be associated with reflex nervous changes, whether or not the immediate changes after embolism were due to this.

Eleven dogs were successfully studied in detail following repeated injections of specific amounts of starch saline suspension into the superior vena cava to produce generalized pulmonary embolism and finally death. Many previous investigations of pulmonary embolism disregarded the dose of material in relation to area or volume of the arterial system. Griffin and Essex in 1949 did use a dose by weight plan to determine minimum lethal starch dosage for dogs. This proved to be .5 cubic centimeter per kilogram of a 1:2 corn starch suspension. We used several dosage scales at first, but soon settled on 50 milligrams per kilogram as the usual increment of starch in studying the effects of repeated doses and in determining the lethal dose. Figure 6 shows the data from these 11 animals which were given multiple doses of starch to final death. The solid lines indicate the average of the curves while the total shaded portion indicates the variation. In this series, the average lethal dose was 204 milligrams per kilogram starch with a lethal dose range of 165 to 335 milligrams per kilogram. The point at which each heavy line changes greatly was the last (average) dose which was well tolerated with survival and the next and last point indicated by the heavy lines shows death of the animal. Figure 6, therefore, shows increasing respiratory rate and decreasing pulse rate at the same time that the aortic blood pressure falls and pulmonary artery pressure rises. The superior caval pressure showed slight increase but no great rise until the last dose leading to death was administered. Figure 7 illustrates the relation between the percentage of the eventual lethal dose of starch and the measured pressure in the pulmonary artery. The broken line represents the average of the individual curves. The initial slope steepened as larger percentage doses were received, but in general, the pressure in the pulmonary artery increased steadily until the last dose prior to the lethal one—which resulted in death and abrupt lowering (not shown) of pressure. In 6 of 7 dogs pressure increased steadily to 29 millimeters of mercury or greater before death. In the seventh it was rising steadily but showed an abrupt decrease at the close, representing 87.5 per cent of lethal dose. The difference from all others suggests a measurement error.

TABLE I.—SIMILARITY OF TOTAL LETHAL STARCH DOSAGE BETWEEN STANDARD SERIES AND SERIES WITH 1 HOUR ELAPSING BETWEEN DOSES

"Standard" series, mgm./kgm.	*"1 hour between doses" series, mgm./kgm.*
125	275
165	200
175	275
175	150
170	175
175	275
202.5	100
200	200
220	200
300	
332.5	
Average 204	206

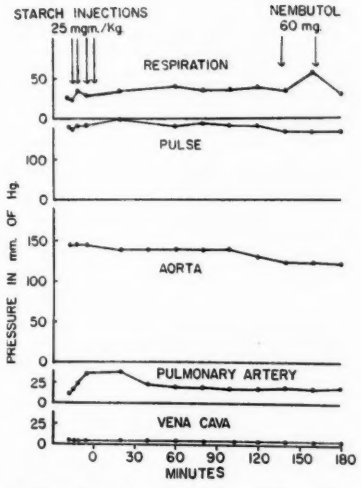


FIG. 5. Data following 4 injections of 25 milligrams per kilogram starch into the superior vena cava to produce general embolism.

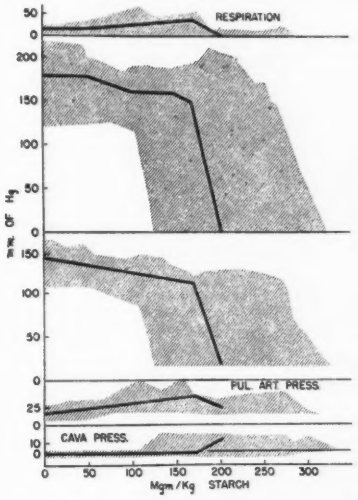


FIG. 6. Average of 11 anesthetized dogs receiving repeated doses of starch until death. Solid line is average. Shaded portion shows range of data.

These 11 animals appeared to follow a consistent pattern of increasing pulmonary hypertension and increasing systemic hypotension with systemic venous hypertension occurring just prior to death. These effects have been observed previously. Dunn in 1920 studied starch embolism in goats, reporting systemic hypotension and venous hypertension followed by death. Later studies elaborated these findings and in 1942, Megibow, Katz, and Steinitz constructed a detailed diagrammatic hypothesis of pulmonary arterial bed obstruction leading to rapid right heart failure. Holden, Shaw, Cameron, and Shea in 1949 studied 40 dogs with actual blood clot emboli and concluded that pulmonary arterial obstruction best explained death without evidence of important reflex changes. Our "standard" studies, therefore, appear to confirm these previous reports.

In our experiments the time between doses of starch varied and actually depended upon the early stabilization of pressures, so that as soon as that occurred, subsequent injection was given. Because the time variation between injections might have a bearing upon the final outcome, this particular factor was evaluated in a new series of 9 dogs. Each of these animals initially received 50 milligrams per kilogram of starch into the superior vena cava with subsequent similar doses at 1 hour intervals until a total of 150 milligrams per kilogram had been given. Thereafter, the dose was 25 milligrams per kilogram at 1 hour intervals until death. The average lethal dose of starch for these 9 animals was 206 milligrams per kilogram of starch (Table I). This approximates the average lethal dose of 204 milligrams per kilogram starch in the previously studied "standard" series of 11 animals and appears to indicate that lengthening the time period between the graded doses to 1 hour did not affect the tolerance of the animals to the multiple pulmonary embolization. It is quite conceivable that longer time intervals might change the tolerance to the injections of starch, but that factor did not seem to enter into the problem of quickly repeated doses and, therefore, was not studied.

Glass beads as emboli. Particularly in view of

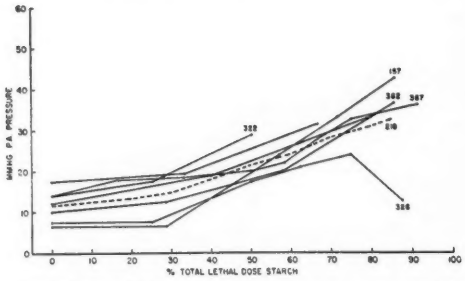


FIG. 7. Correlation of pulmonary artery pressure with the administered dose of starch in terms of percentage of eventual lethal dose. Numbers refer to individual dogs.

Whitteridge's hypothesis that reflex effects might be dependent on the site of obstruction of the pulmonary arteriole (that is, the relation of site of lodgment in arteriole to position of afferent nerve endings), it appeared desirable to test emboli of several sizes. Glass beads were obtained in various diameters and those of 100 and 500 microns in diameter were used.

Initially, 4 dogs received 100 micron beads in repeated doses of 50 grams per kilogram until death. Difficulty in getting beads to flow through the catheter into the dog were finally overcome by passage of a very large catheter. The lines marked 399 and 483 in Figure 8 represent animals into whom the beads were injected via the jugular vein. Animals 30 and 506 had injection via a catheter lying in the right ventricle. The larger lethal doses of 399 and 483 indicate that injection of beads into the vena cava resulted in trapping of part of these beads in the right ventricle so that a smaller dose was actually received by the lungs. For instance, dog 483 received a total of 13.5 grams of 100 micron beads via the jugular vein, but only 6.85 grams of beads were recovered from both lungs after maceration. On the other hand, if the catheter was put into the right ventricle, the total dose essentially went into the lungs as in dogs 30 and 506.

TABLE II.—AVERAGE VOLUME (3 TRIALS) OF 4 GRAMS OF EMBOLIZING SUBSTANCES

Material	*Average volume, c.c.*
Corn starch	2.67
$BaSO_4$	1.03
Glass beads	
100 micron	1.61
500 micron	1.58
1000 micron	1.57

Nevertheless, the pattern of response of all these appears similar. Systemic hypotension and pulmonary hypertension occurred in progressive fashion as repetitive doses were given and was similar to the response after starch embolism. The caval hypertension did appear to occur sooner than when starch was used. We could, therefore, detect no qualitative difference in the pattern of the phenomena occurring after the small starch or larger glass bead embolism.

The lethal dose of 100 micron glass beads was in these experiments greater than that of starch. While this might be due to several factors, it is thought that the difference in lethal doses could be related to the difference in density of the emboli, so that it would take a greater weight of a denser material to block the same cross section of the arterial system as a lighter material.

Four grams of beads were placed in the bottom of a 10 cubic centimeter volumetric flask and water carefully added from a pipette to determine the volume of water necessary to reach the mark. From this was calculated the volume of the beads. Table II shows the average results of 3 trials, each to determine the volume of similar weights of starch and several bead sizes. Theoretically, all sizes of the beads should displace the same volume by weight independent of their diameter, since their density is the same. The similarity of test results in Table II indicates the accuracy of the method.

Table II indicates that 4 grams of starch were larger than 4 grams of beads (by 2.67 : : 1.60 ratio), indicating the beads to be denser than the starch. The denser beads might be expected to require a greater weight dose to block the same pulmonary volume as occluded by a lesser weight of lighter starch. Calculations show that the actual volume of the lethal doses of 100 micron beads, injected via the catheter in

the ventricle to prevent ventricular pooling, were near the theoretic dose necessary to form the same volume as the starch. The average lethal starch dose was 204 milligrams per kilogram.

$$\frac{\text{L.D. volume starch}}{\text{4 gm. volume starch}} = \frac{\text{L.D. weight starch}}{\text{4 gm. weight starch}} \quad (1)$$

$$\text{L.D. volume} = \frac{(\text{L.D. weight})\ (\text{4 gm. volume})}{\text{4 gm. weight}} \quad (2)$$

$$\text{L.D. volume} = \frac{(204\ \text{mgm.})\ (2.67\ \text{c.c.})}{4000\ \text{mgm.}} \quad (3)$$

$$\text{L.D. volume} = .136\ \text{c.c. starch/kgm.}$$

If 4 gm. of 100 micron beads constitute 1.61 c.c., then .136 c.c. should weigh:

$$\frac{0.136}{1.610} \times 4000 = 338\ \text{mgm.} \quad (4)$$

The predicted lethal 100 micron bead dose, then, is 338 milligrams per kilogram on the basis of volumetric comparison.

Only 2 experiments are available for this comparison, namely 30 and 506 in Figure 8. Other experiments were either unsuccessful because of failure to get all beads into the lungs or for other technical reasons. The 2 available show lethal doses of 350 and 400 milligrams per kilogram respectively. It is not statistically significant to compare these 2 results with the calculated prediction of 338 milligrams, but this approach may prove of value in attempting to determine whether emboli of different materials can be related upon the basis of their volume, and so the amount of pulmonary vascular bed expected to be blocked.

Experiments using 500 and 1,000 micron glass beads have been unsatisfactory to date, chiefly because of difficulty in getting the beads through a cannula into the lung and preventing their pooling in dependent portions due to gravity rather than scattering widely. The use of plastic beads whose density is nearer that of blood might prevent this trouble. The large bead experiments showed a similar pattern of response, but very large amounts were usually necessary to kill the dog, and autopsy showed extensive piling up of the beads in a few vessels with poor diffusion so that "general" embolization was not uniform.

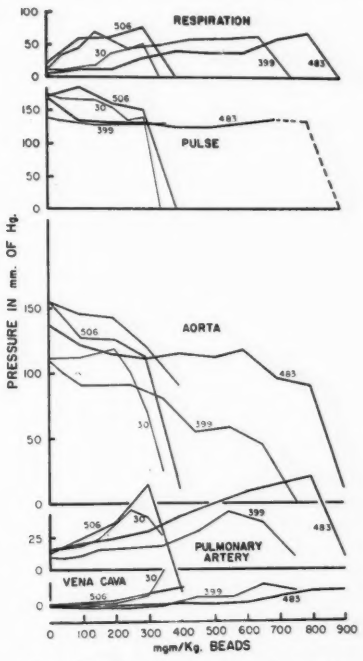


FIG. 8. Data following repetitive injection of 100 micron glass beads to produce generalized embolism. Dogs 399 and 483 had catheter in vena cava while dogs 30 and 506 had catheter lying in ventricle, so most of each dose reached the lungs.

The effect of bilateral cervicothoracic sympathectomy. Bilateral cervicothoracic sympathectomy was performed prior to starch embolization in 4 dogs to determine whether the basic pattern of response, as determined previously, could be altered by removal of this autonomic influence. Figure 9 shows the individual experiments (solid lines) compared to the average of the "standard" series (broken lines). The average lethal dose for these 4 sympathectomized animals was 201 milligrams per kilogram as compared to 204 milligrams per kilogram for the 11 standard dogs. We could detect little difference in the response to graded doses of starch after sympathectomy. The respiration pattern was reproduced in approxi-

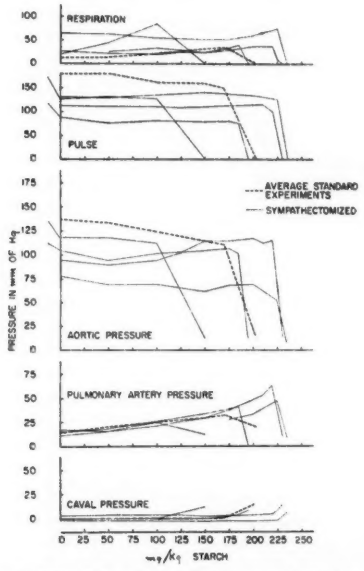


FIG. 9. Four bilaterally sympathectomized dogs with repeated starch embolism (solid lines) compared to average of standard starch embolism series (broken lines).

mately the same manner. Following sympathectomy, there was a decrease in pulse rate, and this rate was perhaps maintained somewhat better than in the standard series but again fell terminally prior to the final bradycardia and death. The pulmonary artery pressure still rose in a stepwise fashion, and this closely paralleled the standard animals. Although Villaret, Justin-Besancon, and Bardin found that sympathectomy in rabbits reduced lethal dose of pumice stone to one-fourth the control dose, we found no particular changes in this series and judged that the reflex changes must be searched for by another method.

The effect of bilateral cervical vagotomy. Bilateral cervical vagotomy was performed in 4 dogs prior to starch embolization (Fig. 10). The respiratory rate was slowed by this procedure. After embolization the responses were similar to the standard series. Again there was a stepwise progression in the pulmonary artery pressure. The superior vena caval pressure performed similarly to the standard series. The average lethal dose of starch was slightly less in this series than in the standard series, but the range was similar. This observation agrees with those in the reports of Griffin and Essex and Holden, Shaw, Cameron, and Shea who found no important change after either sympathectomy or vagotomy. Villaret, Justin-Besancon, and Bardin reported in 1936 that rabbits tolerated 7 times more pumice stone emboli after vagal section than before. Our results are contrary using a different animal and different embolizing material.

The effect of papaverine administration. Three dogs received graded doses of starch and multiple doses of intravenous papaverine, ranging from .016 to .032 gram per dose and a total dose varying between .065 and .080 gram. In each instance, the administration of papaverine caused a simultaneous sudden decrease in pulmonary artery pressure and aortic pressure with little change in vena cava pressure; however, the plot of the total pressure curves in these animals (solid lines in Fig. 11) remained similar to the average standard preparations (broken lines in Fig. 11). The lethal doses for the 3 animals were 175, 227, and 279 milligrams per kilogram of starch. It appeared that intravenous papaverine caused a generalized decrease in pressure within all vessels, presumably due to loss of vascular tone. Jesser and DeTakats in 1941 reported radiographic evidence of widening of the pulmonary artery following barium sulfate embolism and papaverine in dogs. This, no doubt, occurs, and our data showing pressure drops tend to corroborate the report, but we found only a transitory effect after even repeated papaverine administration. There was almost immediate compensation following pressure decreases, and we could detect no over-all improvement in the pattern of the 3 dogs which had received papaverine. One animal immediately became apneic with severe general hypotension following administration of papaverine and with a prolonged recovery. This experience, along with the lack of good effect in the other 2 animals, led us to be-

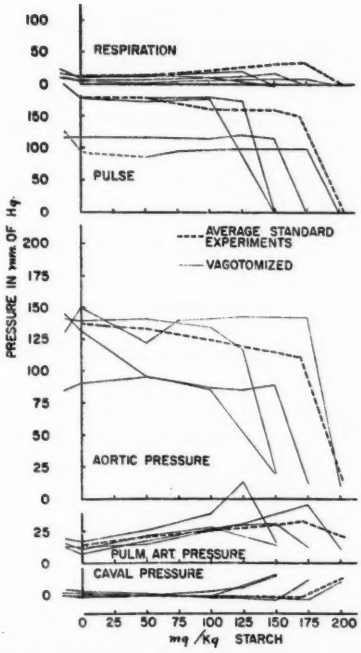


FIG. 10. Four bilaterally vagotomized dogs with repeated starch embolism (indicated by the solid lines) compared to average of the standard series (indicated by the broken lines).

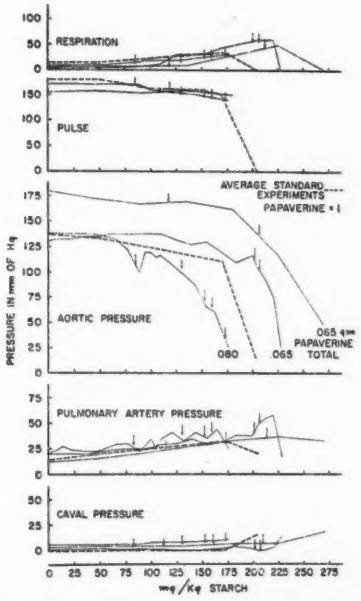


FIG. 11. Three dogs receiving intravenous papaverine injections (at each arrow on aortic pressure curve) after starch embolism with total papaverine dose at end of curve. Broken lines show average of standard series.

lieve that under the conditions of the experiment, papaverine does not increase the tolerance of the animal to starch embolism.

DeTakats, Beck, and Fenn in 1939 reported gross mortality rates following embolism by starch and believed that atropine and papaverine exerted a protective effect by blocking reflex spasm. Holden and associates in 1949 reported that papaverine caused little change after embolism except for a transient reduction in right atrial pressure. Our experiments appear to corroborate these findings, and the drug was, therefore, not used further.

The effect of atropine administration. Villaret, Justin-Besancon, and Bardin reported that rabbits with intact vagi were protected after pumice stone embolism so that death was delayed (although not prevented) by use of atropine and ephedrine.

Four dogs were studied by producing repeated starch embolism (50 mgm./kgm. every hour) until death. In addition, each dog received 1 milligram per kilogram atropine sulfate intravenously 5 minutes prior to the first emboli injection. The total lethal starch doses were 150, 100, 150, and 150 milligrams per kilogram, an average of 133 milligrams per kilogram which is certainly no improvement over the 206 milligrams per kilogram average lethal dose for the control series, shown in Table I.

In summary then, neither bilateral cervicothoracic sympathectomy, bilateral cervical vagotomy, intravenous papaverine, nor intravenous atropine appeared to influence the pattern of response, nor appreciably change the lethal dose of graded starch pulmonary embolism. This observation furnishes arguments against the importance of

reflexes mediated via either the sympathetic or parasympathetic nervous system in these experiments. In each instance of the total series, the cardiovascular response appeared to be one of increasing pulmonary hypertension and systemic hypotension. The heart appeared able to compensate for the increased pulmonary resistance up to a given point beyond which there was rapid failure and death.

The effect of reduction of total pulmonary arterial volume. Since we were unable to find important reflex effects in the cited experiments, it was postulated that the actual cause of death was heart failure due to increased pulmonary arterial resistance caused by obstruction by the particles, with probable later development of thromboses in these areas.

Haggart and Walker in 1923 reported the effects of quantitative closure of portions of the pulmonary artery in cats, finding that about 60 per cent luminal occlusion could be produced prior to a significant decrease in the systemic pressure. Death always followed 85 per cent occlusion. We, therefore, predicted that production of such pulmonary arterial occlusion should cause decrease in the total starch dose necessary to kill the animal. Six animals were initially prepared by placing a simple ligature on the left main pulmonary artery and 5 more by placing a simple ligature on the right pulmonary artery. Each of these animals could then be embolized into a reduced pulmonary vascular area without possibility of scatter of the emboli into the other portion of the lung. Figure 12 is the plot of these experiments. The vertical scale shows per cent of pulmonary arterial bed left open after a ligation of part of it. The original "standard" animals were used to represent the lethal doses of starch in animals with 100 per cent pulmonary arterial volume and point *a* on the graph is the average 204 milligrams per kilogram lethal starch dose. Two methods were used to determine the reduction in pulmonary volume after tying off one of the pulmonary arteries. The lungs were both carefully removed at the termination of the experiment and following inflation to a given pressure, the amount of air contained within was measured by aspiration. This, then, determined the proportion of air contained in each lung and, therefore, their relative volumes. However, because of technical difficulties, this method was abandoned and the second method actually used to calculate the proportion of lung which had been removed from the pulmonary arterial circulation. This consisted of simply weighing each lung after its careful removal, at which time all vessels were tied with individual silk ligatures. This had the advantage of simplicity. Criticism may be directed at the method because the embolized lung probably contained some amount of thrombus, which cannot be measured. We have assumed the weight of thrombus to be insignificant in relation to the entire lung weight.

The plot shows good separation of points representing "standard" embolizations contrasted to those representing dogs who had part of their pulmonary arterial bed removed by ligation. The dogs with left pulmonary artery ligated showed somewhat larger lethal doses of starch because the remaining open portion of the pulmonary arterial bed was larger. Previous studies here have shown the greater weight and oxygen uptake capacity of right over left lung (2) and it can be assumed that the pulmonary arterial volume parallels this.

Point *b* in Figure 12 represents the ultimate resection of pulmonary tissue which will allow survival of the dog as determined by Schilling. Death resulted in 100 per cent if he removed more than 83 per cent of the total lung tissue (17 per cent remaining). The broken line in Figure 12 connects this point *b* with point *a* (average lethal starch dose in the standard series). If mechanical obstruction of the pulmonary vessels alone, or chiefly, results in death, we would expect the points to fall along this line. If reflexes add to the ill effects of pulmonary vascular obstruction, we would expect the points to

form an experimental curve dissimilar to the predicted line. We interpret the data as tending to reproduce the predicted line *a-b* and so to indicate the importance of pulmonary vascular obstruction rather than reflex effects in the deaths from starch embolism in these experiments.

Localized Embolism

Localized starch pulmonary embolism. Since study of generalized pulmonary embolism failed to show evidence of important reflex effects, experiments in which the emboli were localized to a part of the lung were made to attempt detection of reflex changes in the unembolized part of the lungs.

Haynes, Kinney, Hellems, and Dexter in 1947 reported that slow infusion of lycopodium spores into a lobar artery (blocked proximal to the injection site by an inflated balloon) regularly produced tachypnea, pulmonary hypertension, systemic hypotension, and terminal venous hypertension ending in death. Vagotomy and pithing the spinal cord did not prevent these phenomena.[1]

Hara and Smith in 1949 reported that obstruction of the lobar arteries and smaller branches (.5 mm. diameter) by glass beads or poppy seeds produced no significant cardiocirculatory effects if widespread mechanical block was avoided. Cate, Light, Daniel, and Edwards in 1953 found systemic hypotension, bradycardia, and tachypnea after embolism localized to a lobe by injecting beyond an intraluminal balloon. There was no pulmonary hypertension after localized embolization as there was after generalized embolism. Price, Hara, and Smith in 1955 prepared dogs as heart-lung-head preparations and injected barium sulfate as the embolizing material. Pulmonary hypertension decreased and survival time increased when the "head" part was taken out of the preparation by ligation of its arterial supply. They interpret the experiments as evidence of neurogenic pulmonary vasoconstriction. No data are presented on the effect of denervating the preparation without embolism, and it is possible that control denervation without embolism might lower the pulmonary pressure. The 5 published protocols indicate central denervation to have been done immediately after the embolism produced pulmonary hypertension at the height of response, 1 minute, 30 seconds, 6 minutes, 5 minutes, respectively. Our Figure 4 indicates that these times are all within the expected early recovery phase. Further, the pulmonary pressure decreases of Price and associates are small.

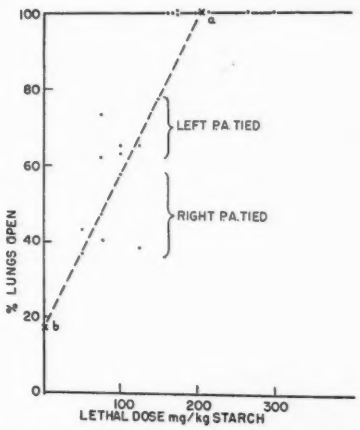


FIG. 12. The effect of decreasing the total pulmonary arterial bed, by ligation of part, in reducing the lethal starch dose.

Niden and Aviado in 1956 reported that perfusion of the left lower lobe artery and embolization of the other lung caused a pulmonary pressure rise in the isolated perfused lobe which could be prevented or greatly decreased by combined sympathectomy and vagotomy. This observation appeared to indicate pulmonary vasoconstriction as the result of glass bead embolization. With these reports of localized embolism as background, starch embolism to the left lower lobe was studied.

Slow injection of starch granules into the left lower lobe via a transcardiac catheter

[1]Dexter in a recent letter, however, commented upon the "scatter" which almost always occurred in their dogs, so that only a preliminary report of their work was made and those reported conclusions may not be warranted.

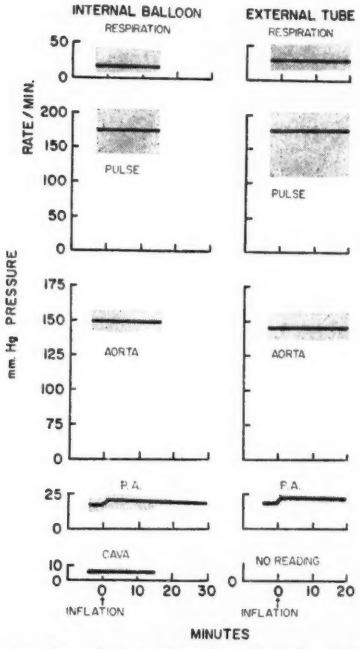


FIG. 13. Data obtained following left main pulmonary artery occlusion by internal balloon (left) and by external compression (right). Heavy lines represent average and shaded portions show range.

soon showed reflux of the starch into other parts of the lung, as determined by microscopic examination under polarized light which made the starch granules shine clearly (Fig. 1). Inability to localize the emboli by this method led to the internal balloon occlusion method used by Cate and associates.

Ten experiments with the balloon inflated in one of the main pulmonary arteries indicated that the effect of the balloon itself was to produce an immediate change in oxygen consumption of the two lungs as evidence of shifted blood flow due to pulmonary vascular occlusion. This tended to remain constant over a 60 minute period, relatively small changes being thought due to variations in the recording apparatus and in the measurements.

Figure 13 shows the average (solid line) and variation (shaded) of the respirations, pulse, aortic pressure, pulmonary artery pressure, and vena cava pressure of dogs that had had one of their pulmonary arteries occluded. On the left the occlusion was by an internal balloon passed through the heart prior to inflation (shown in Fig. 2). The right part of the figure shows data when the artery was blocked by the external tube device (shown in Fig. 3). There appears no difference between the data, indicating the same results whether the occlusion was due to internal balloon occlusion or to external tube compression. In fact, no change occurred at all except for a small increase in pulmonary artery pressure which slowly declined.

Previous work has reported similar results of balloon occlusion of the pulmonary arteries. Cate, Light, Daniel, and Edwards found return of initial elevation to control levels of pulmonary artery pressure at the end of ten minutes. Nemir, Stone, Mackrell, and Hawthorne studied 10 humans and found that 30 to 40 minutes after balloon inflation the pressures of all were within 10 millimeters of control values with a single exception.

Twelve experiments were done by injection of starch distal to a balloon inflated in the pulmonary artery. In all, the emboli remained localized as proved by polarized light slide microscopic examination. Others, later microscopic sections of which showed reflux into other parts of the lungs, were discarded. *Slide examination under polarized light clearly indicated that such reflux could occur, even though the balloon be inflated.* Assumption of localization of emboli is thus improper without examination, and the polarized light microscopic examination greatly facilitates this. Reports of other experiments in which this examination was not done, or was difficult to do accurately, may not show data on emboli strictly localized to one lobe.

Figure 14 contrasts the results of 14 proved localized starch embolizations (10 by internal balloon and 4 by external tube occlusion of artery proximal to injection) with generalized starch embolism (single dose). Control data were made prior to artery oc-

clusion. The artery was then occluded, starch injected, and the balloon or tube deflated. The next reading of the Sanborn polyviso recorder was made just after release of the mechanical occlusion of the artery.

No pulse change occurred in either series.

No immediate respiratory change occurred in localized embolism, although the dogs which had open thoracotomy for tube placement later showed increasing respiratory rate. Tachypnea, however, began at once with general embolism.

Aortic pressure sharply decreased and then slowly returned after general embolism. The average slight rise and immediate fall following localized embolism was unexpected. This average was produced by certain dogs showing this response which was calculated into the curve with the others showing no change at all. This is probably explained by increased return to left ventricle due to the injection. Saline injection alone would at times reproduce this effect.

Vena cava pressure did not change in either group.

Pulmonary artery pressure increased after general embolism and changed very little over the 1 hour observation period, although some animals showed compensation within this time, and as Figures 4 and 5 show, a compensatory decrease was expected. Localized embolism produced a small rise in pulmonary arterial pressure which averaged 3.5 millimeters of mercury in these animals, while general embolism caused an average rise of 7.5 millimeters of mercury. The balloon occlusion in Figure 13 produced an average of about 3.5 millimeters of mercury also, so we conclude that the balloon blockade was simply replaced by the starch injected distal to it. In other words, balloon release did not open a part of the pulmonary arterial bed to blood flow, since starch particles blocked that part.

Examination of the individual dog's data as well as the averages of Figure 14 fails to show evidence of reflexes triggered by starch in a lobe and, instead, supports a mechanical explanation of the response.

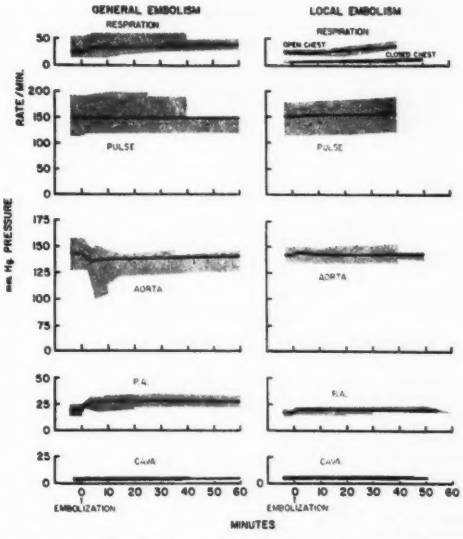


FIG. 14. Comparison of data from 14 localized embolism experiments and generalized embolism experiments.

The report of Cate, Light, Daniel, and Edwards showed "systemic arterial hypertension, bradycardia and tachypnea . . . following localized embolization," results which differ from ours. The question of whether localization was complete must be raised, since our experience indicates that reflux passage into other parts of the lung can occur even when an internal balloon is present to block this. Lewis Dexter (8) has recently stated (by letter) that their group has also had difficulty localizing lycopodium spores to one lobe. Future experiments should be carefully appraised in regard to this reflux. When starch is the embolizing substance, the polarized light microscopic examination is quite superior to the usual method of looking at slides.

In several dogs the embolizing material was changed to lead phosphate-agar gel as described by Schlesinger and used by Cate and associates. Using the latters' dosage, as well as one-half and one-third that dosage, did not prevent reflux in our experiments. The reflux appears the explanation for the

pulmonary and systemic pressure changes found in the 3 dogs we studied with this material. Because of inability to localize the gel, it was not used any more.

Measurements of the oxygen consumption recorded separately from each lung show the relative blood flow of 2 lungs. A previous series of 12 dog studies here showed the right lung to average 56 per cent of the total oxygen consumption and the left lung, 44 per cent. This compared well to the data of Rahn and Bahnson (using a different type lung divider) where the ratio was 58 to 42. This appears to represent also the average ratio of blood flow to the two lungs, the left being somewhat smaller because the heart lies more on that side.

It was postulated that if there were pulmonary vasoconstrictive reflexes secondary to pulmonary embolism, these might alter the pulmonary vascular resistence in the nonembolized upper lobe on the side of the locally embolized lower lobe more than in the contralateral side. Emboli to the left lower lobe should shift the blood flow ratio (and therefore, the oxygen consumption ratio) at once, since part of the left lung arterial bed was blocked. If further shift of this ratio occurred after the immediate change at time of embolization, it would constitute evidence for further cumulative reflex vasoconstriction.

The oxygen consumption ratio was studied in 7 dogs subjected to localized starch embolism. Figure 15 shows the constant occurrence of shift in oxygen consumption ratio when emboli were injected into the left lower lobe. The graph indicates this as a sharp decrease in the percentage of oxygen consumption of the left lung in each experiment. Six of the 7 were followed for 120 minutes and the other for 60 minutes. There is minor variation of the oxygen consumption percentage after the initial embolization shift. In all except 1 this is within 8 per cent. We interpret Figure 15 as failing to provide positive evidence for localized ipsilateral increase in pulmonary resistance in the upper lobe. Failure to demonstrate this may indicate that (1) there is no important reflex vasoconstriction, (2) if vasoconstriction occurs, it is equal in both ipsilateral and contralateral arterial systems, or (3) the technique is not sensitive enough to detect small changes. While the latter may be true, we believe that great unilateral vasoconstriction does not occur, although minor degrees of it may.

Reflection of embolism effect in perfused lobe. Niden and Aviado's recent report that embolism of the lung is reflected by a pressure rise in a perfused lobe is convincingly attested by their photograph of a pressure tracing. Since we had been unable to find evidence for important reflex effects by the methods discussed, it was decided to attempt repetition of the Niden-Aviado experiment; and one of us (R. M.) visited Doctor Aviado and discussed this technique and its results, although an actual experiment was not observed. Subsequently, 7 different perfusion experiments were performed, omitting many early failures due to technical defects.

Initially, the left pulmonary artery was transected at its easily accessible location, i.e., between the left middle lobe (lingula) and the left lower lobe, and plastic or glass cannulas were inserted into the ends of the artery, one proximally to allow measurement of pulmonary arterial pressure and one distally to allow perfusion of the left lower lobe. The venous drainage of the left lower lobe was isolated but proved to be a difficult dissection as the lobar veins are short after the branches join peripherally, and it was technically difficult to secure a cannula in the left lower lobar vein. Further, if the left lower pulmonary vein was cannulated, pulmonary edema rapidly ensued and the preparation was unsatisfactory for study of pulmonary arterial pressure and blood flow. This has been also reported in extracorporeal shunt experiments.

Later, no attempt to drain blood from the left lower lobar vein was made, except to allow it to pass by normal channels to the left atrium. This has the theoretic disad-

vantage that emboli might pass via arteriovenous shunts in the right lung into the systemic circulation, thence into the donor dog and into the perfused lobe; but in our few satisfactory experiments we did not find evidence of this.

Niden and Aviado's report of the importance of intrapericardiac dissection to preserve nerve supply to the lobar vessels was noted, and the following preparation was made. In the recipient dog, catheters were placed via the right femoral vessels to lie in the aorta and inferior vena cava to allow recording of aortic and venous pressures. A catheter was inserted into the left femoral artery to allow withdrawal of blood of volume approximately equal to that which was used to perfuse the left lower lobe. The donor dog was anesthetized with sodium pentobarbital, and catheters were inserted into the femoral vessels to allow withdrawal of venous blood for perfusion of the lung and returned via the femoral artery. A Sigmamotor pump (T-4) was used to regulate flow of blood between donor and recipient dogs. The left pulmonary artery was isolated by intrapericardial dissection. While this was technically difficult in the first cases because of major hemorrhage during dissection of the artery, it was not a problem after development of technique. This method allowed interruption of flow of blood into the left pulmonary artery and use of the lateral aspect of the main pulmonary artery for insertion of catheters to record pulmonary arterial pressure and to insert emboli. These catheters were secured via purse-string sutures or multiple interrupted sutures. This approach allowed very satisfactory pressure recording and injection of emboli into the right pulmonary artery.

Alternately, the lobar artery to the left upper lobe was isolated and was of sufficient length so that a cannula could be inserted and the left lower lobe perfused with blood. The ligature was peripheral on the upper lobar artery so that there was no ligature or pressure about the extrapericardial portion of the left pulmonary artery. The lobar artery to the middle lobe was ligated.

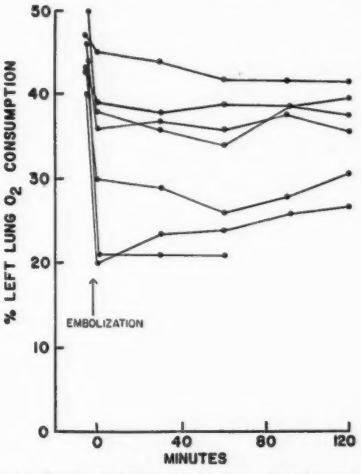


FIG. 15. Seven experiments to show the change in left lung oxygen consumption following localized left lower lobe starch embolism.

The recipient and donor dogs were heparinized with aqueous heparin (1 mgm. per kgm.) approximately 5 minutes before perfusion. This dosage was adequate for the duration of the experiments done and in only 1 animal was there bleeding, and that was about one of the catheters into the main pulmonary artery after the pressure had increased to 60 millimeters of mercury.

It was found important to begin perfusion at a relatively low flow rate, as there appeared to be increased pulmonary resistance after this dissection about the pulmonary artery and its branches. However, within a few minutes the flow rate was gradually increased, and a level was established that would maintain a left lower lobar arterial pressure of 13 to 15 millimeters of mercury, a level approximately equal to that in the right pulmonary artery. The pressure in the left lower lobar artery was recorded via a T tube leading off the tubing just outside the chest and at the same height as the lobar artery.

Blood was withdrawn from the left femoral artery of recipient dog in amounts equal to that used to perfuse and returned to the

donor dog via the Sigmamotor pump. Mayon plastic tubing was used.

Injection of starch into the right lung now invariably elevated the right pulmonary pressure, as expected. We were, however, never able to record a change in the left (perfused) lobe pressure. Although it is difficult to doubt the published tracing of Niden and Aviado and our technical inability to reproduce this is possible, it is noted that Williams has similarly reported inability to produce perfused lung changes by embolism. Further investigation of this observation is in order. Whether the Niden and Aviado effect is great enough to be of importance clinically is, of course, another and larger question. Failure of sympathectomy or vagotomy to change our experimental mortality points to probable failure of drugs affecting these nerves to alter clinical conditions.

COMMENT

Review of the literature, with a few exceptions, fails to provide convincing evidence of important reflex effects of pulmonary embolism. The resultant tachypnea is undoubtedly eventually due to central stimulation by reflex or by blood chemical changes, but the respiratory rate and tidal change per se does not appear lethal or even dangerous. Previous discussion of dangerous reflexes has centered about possible widespread pulmonary vasoconstriction triggered by emboli which by their size alone would not be dangerous. Earlier reports of such often followed experiments in which animals lived somewhat longer after drug treatment or autonomic nerve block or surgery, or were based on different survival rates in small groups of animals with and without treatment. The experiments cited before showed no difference in the pattern of response to starch embolism after either autonomic nerve surgery or the use of papaverine or atropine, nor any increase in the lethal dose of starch.

Other reports have centered upon localized embolism and its effects upon the nonembolized lung. Our experience with difficulties in insuring localization indicate that such experiments must be carefully studied at postmortem examination to be sure that general spread has not occurred. Failure to note such spread may explain certain reported evidences of widespread effects of localized embolism. The most convincing evidence yet seen is the Niden and Aviado report of lung perfusion commented upon before. We are unable to explain why our experiments failed to reproduce the effect shown in their pictured record.

We interpret our experiences as failing to show evidence of important reflex effects or of reflex pulmonary vasoconstriction secondary to localized embolism. In addition, there are certain data which indirectly at least, rule against important reflex effects of embolism. Failure to change either pattern or lethal doses by drugs or autonomic surgery tends to rule against sympathetic or parasympathetic reflexes. Graded lowering of lethal dosage by reduction of pulmonary arterial bed appears to indicate the lethal dose is due to mechanical blockade of the pulmonary arterial system. Finally, the failure to find evidence of pulmonary arterial vasoconstriction after either localized embolism or during lobar perfusion experiments indicates that starch in anesthetized dogs fails to produce important reflex effects.

All the pressure records show the same pattern of increasing pulmonary hypertension, slower systemic hypotension, and final venous hypertension which has been previously reported. This observation leads to the conclusion that right heart failure occurs as the terminal event and is due to pulmonary hypertension occasioned by mechanical blockage of capillaries and arterioles.

It must, of course, be emphasized that these experiments upon anesthetized dogs do not necessarily hold for nonanesthetized dogs, since it is reported that anesthesia results in a different dose tolerance of emboli from nonanesthetized animals. The pattern

of response of the pressures in nonanesthetized animals was not studied, and it might be argued that anesthesia prevents certain reflex phenomena. Decerebrate nonanesthetized animals might be useful for further studies in this connection.

It should be further emphasized that starch or bead embolisms are not necessarily productive of the same response as from actual blood clots. However, reports of such experiments have not shown any real differences in the pattern of response from those produced by starch and beads, so long as the size is approximately the same.

SUMMARY

Experiments on anesthetized dogs with starch and glass beads as pulmonary emboli are reported with comments upon certain previous similar studies. No evidence for important reflex phenomena could be found. The data are interpreted to indicate that such emboli cause pulmonary arterial bed obstruction with resultant pulmonary hypertension followed by systemic hypotension as left ventricular output decreases, and with late venous engorgement and right heart failure leading to death.

REFERENCES

1. Cate, W. R., Jr., Light, R. A., Daniel, R. A., Jr., and Edwards, W. H. Role of the autonomic nervous system in the control of the pulmonary vascular bed. Surgical Forum, 1952; American College of Surgeons. P. 190, Vol. III. Philadelphia and London: W. B. Saunders Co., 1953.
2. Dale, W. A., and Rahn, H. Experimental functional separation of dog lungs. J. Thorac. Surg., 1955, 29: 453.
3. DeTakats, G., Beck, W. C., and Fenn, G. K. Pulmonary embolism: an experimental and clinical study. Surgery, 1939, 6: 339.
4. Dunn, J. S. The effects of multiple embolism of the pulmonary arterioles. Q. J. Med., Oxf., 1920, 13: 129.
5. Griffin, G. D. J., and Essex, H. E. Experimental pulmonary embolism of the pulmonary arterioles and capillaries. Surgery, 1949, 26: 707.
6. Haggart, G. E., and Walker, A. M. The physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery. Arch. Surg., 1923, 6: 764.
7. Hara, M., and Smith, J. R. Experimental observations on embolism of pulmonary lobar arteries. J. Thorac. Surg., 1949, 18: 536.
8. Haynes, F. W., Kinney, T. D., Hellems, H. K., and Dexter, L. Circulatory changes in experimental pulmonary embolism. Fed. Proc., Balt., 1947, 6: 125.
9. Holden, W. D., Shaw. B. W., Cameron, D. B., and Shea, P. J. Experimental pulmonary embolism. Surg. Gyn. Obst., 1949, 88: 23.
10. Jesser, J. H., and DeTakats, G. Visualization of the pulmonary artery during its embolic obstruction. Arch. Surg., 1941, 42: 1034.
11. Lategola, M., and Rahn, H. A self-guiding catheter for cardiac and pulmonary arterial catheterization and occlusion. Proc. Soc. Exp. Biol., N. Y., 1953, 84: 667.
12. Megibow, R. S., Katz, L. N., and Steinitz, F. S. Dynamic changes in experimental pulmonary embolism. Surgery, 1942, 11: 19.
13. Nemir, P., Jr., Stone, H. H., Mackrell, T. N., and Hawthorne, H. R. Controlled unilateral bronchovascular occlusion as a method for studying pulmonary function. Surgery, 1953, 34: 401.
14. Niden, A. A., and Aviado, D. M. Effects of pulmonary embolism on the pulmonary circulation with special reference to arteriovenous shunts in the lung. Circ. Res., 1956, 4: 67.
15. Price, K. C., Hara, D., and Smith, J. R. Pulmonary vasomotion resulting from miliary embolism of the lungs. Am. J. Physiol., 1955, 182: 183.
16. Schilling, J. A., et al. Ann. Surg., in press.
17. Schlesinger, M. J. An injection plus dissection of coronary artery occlusions and anastomoses. Am. Heart J., 1938, 15: 528.
18. Stroud, R. C., and Rahn, H. Effect of O_2 and CO_2 tensions upon the resistance of pulmonary blood vessels. Am. J. Physiol., 1953, 172: 211.
19. Villaret, M., Justin-Besancon, L., and Bardin, P. Recherches sur la prevention experimentale dos accidents consecutifs sur embolies pulmonaires. Bull. Soc. méd. hôp. Paris, 1936, 60: 941.
20. Whitteridge, D. Multiple embolism of the lung and rapid shallow breathing. Physiol. Rev., 1950, 30: 475.
21. Williams, M. H. Some effects of diffuse pulmonary embolism in anesthetized dogs. Walter Reed Army Inst. of Research, 1956, January.

THE RATIONALE OF SUBTOTAL AND TOTAL COLECTOMY IN THE TREATMENT OF CANCER AND MULTIPLE POLYPS OF THE COLON

ROBERT S. GRINNELL, M.D., F.A.C.S., New York, New York

THE RELATIONSHIP of adenomatous polyps and papillary adenomas to cancer of the colon and rectum has received increasing attention in recent years. There is accumulating evidence that if not all, at least nearly all, cancers of the large intestine arise in pre-existing adenomatous lesions. In a recent review of 1,856 polyps and papillary adenomas of the colon and rectum, from the Presbyterian Hospital, New York, Grinnell and Lane have reported that the incidence of invasive cancer is very low, less than 1 per cent, in adenomatous polyps under 1 centimeter in diameter, but that in the larger polyps it increases in proportion to size to over 12 per cent. It is the large polyps and the papillary adenomas that are most important to remove. Recent United States Public Health studies (5) have shown that this cancer ranks first in frequency among males in this country and is close to the top among females, being exceeded only by cancer of the breast and uterus. Consequently, the discovery and removal of these polyps are of the greatest importance as a prophylactic cancer measure.

Many of these polyps, variously reported from 15 to 45 per cent, are multiple, and may be scattered throughout the colon and rectum. Fortunately, approximately two-thirds are within reach of the sigmoidoscope. The discovery of the remaining one-third must depend chiefly on barium enema x-ray films. X-ray diagnosis is frequently inaccurate, especially for polyps less than 1 centimeter in diameter. In 103 patients who underwent colotomy and coloscopy Deddish and Hertz found additional polyps in 46 per cent of the patients which had not been detected in at least 2 preoperative barium enemas. Fortunately, as we have already stated, the incidence of cancer in small adenomatous polyps is very low but if they become large it will be much higher.

Not only are polyps frequently multiple but cancers may be also. The incidence of multiple invasive cancers, excluding patients with familial multiple polyposis, has been variously reported from 1.7 to 8.2 per cent. In 1,083 patients undergoing resection for carcinoma of the colon at the Presbyterian Hospital from 1916 to 1952 inclusive, there were 63 patients with multiple cancers, an incidence of 5.8 per cent. Cases of intramucosal cancer or cancer in situ were not included.

Lillehei and Wangensteen have recently advocated subtotal colectomy with cecorectal anastomosis and total colectomy with ileoproctostomy for patients with multiple polyps of the colon and for those with cancer of the colon in the hope of removing undetected polyps and cancers which might be present and making sure no subsequent cancer can arise. In their hands the operative mortality and morbidity have not been high and bowel function has been satisfactory if not more than 30 centimeters of the terminal ileum are removed when ileoproctostomy is carried out. When multiple polyps are found, Teicher and Abrahams have proposed subtotal colectomy in the presence of: (1) 3 or more polyps in different segments of the colon; (2) 2 or more polyps, any one of which is found on examination to

From the Department of Surgery, Presbyterian Hospital, and the Laboratory of Surgical Pathology, College of Physicians and Surgeons, Columbia University, New York.

contain an adenocarcinoma; (3) a cluster of polyps in any single area of the colon; and (4) when during the course of a colectomy for a solitary polyp further polyps are discovered by palpation of the bowel or by coloscopy. Scarborough has advocated complete colectomy when x-ray examination or coloscopy discloses a single polyp in any 2 of the 3 main segments of the colon. McLanahan and Martin also favor this procedure in selected cases.

It has seemed worth while, therefore, to review the long range follow-up results in patients with multiple polyps and cancers of the colon treated in the past by the usual more conservative procedures and to determine how often subsequent cancers of the colon occurred which might have been prevented had total or subtotal colectomy been carried out initially.

MULTIPLE POLYPS

A survey (2) of all patients with adenomatous polyps and papillary adenomas of the colon and rectum admitted to this hospital from 1928 to 1955 inclusive has recently been completed. There were 1,856 lesions in 1,335 patients with histologic sections and clinical histories available for review. These cases formed the basis for the following study. No cases which were followed for less than 3 years were included. Patients with diffuse familial polypsis were also not included.

Three or more polyps in different segments of colon. This group is the same as that proposed by Teicher and Abrahams and is assumed to include patients with one or more polyps in each of the 3 main segments of the colon. There were 7 cases belonging to this category when the rectum was excluded as one of the segments. Three patients died of unrelated causes and 4 are well. All 7 were followed up for an average of 8 years to an average age of 59 years. The polyps were removed by limited colectomy in 2 cases and by colotomy in the other 5. None of these patients had a subsequent cancer of the colon. From the follow-up results in this small group subtotal colectomy or ileoproctostomy would not have been of benefit.

A single polyp in any 2 of the 3 main segments of the colon. This is the type of case for which Scarborough recommends complete colectomy. There were 9 cases in this group. All of the polyps were removed by colotomy. Four patients died of unrelated causes and 5 are well. All 9 were followed-up for an average of 4 years following operation to an average age of 56 years. None had a subsequent colon cancer and would not have benefited by colectomy.

Two or more polyps with cancer found in any 1 polyp. In this group the cancers were all present in pre-existing adenomatous polyps or papillary adenomas. There were 5 such cases. Two patients died of unrelated causes and 3 are living and well. All 5 have been followed-up for an average period of 7¼ years to an average age of 57 years. Excision was carried out by colotomy in 2, colectomy in 2, and by snare excision in 1. None of these patients had a subsequent colon cancer and none would have benefited by total or subtotal colectomy.

A cluster of polyps of 3 or more in any one area of colon. There were 16 cases in this group. The number of polyps ranged from 3 to 18. Excision of polyps was accomplished by colotomy in 7 patients, limited resection in 5, and snare and biopsy excision in 4. Four died of other causes and 12 are well. All 16 have been followed-up for an average period of 7½ years to an average age of 64 years. One of these patients had 3 polyps of the sigmoid removed by colotomy in 1941. In 1953 a carcinoma of the cecum was discovered and resected. The patient has been well for 4 years since this operation and is now 84 years old.

Two or more polyps with a coexisting cancer of the colon. This group included patients with 2 or more synchronous polyps together with a frank cancer not limited to an early one in an adenomatous polyp or papillary adenoma, as mentioned previously.

There were 15 patients in this group. Four died of unrelated causes and 10 are living.

All 15 have been followed-up for an average period of 7 years following operation to an average age of 68½ years. One patient, however, had a cancer of the cecum with 2 associated polyps resected by ileocolectomy in 1943 and a year later a carcinoma of the sigmoid was discovered and resected. He apparently died from his second cancer 2 years later. This is the only case in which an ileoproctostomy done at the time of the first operation might in retrospect have benefited the patient and prevented the occurrence of the second cancer. Another patient underwent ileocolectomy in 1942 for cancer of the hepatic flexure with 2 adenomatous polyps of the ascending colon and 2 years later was found to have a cancer of the splenic flexure which was also resected. The patient has been well for 6 years since the second operation at the age of 64. No other patient had a subsequent colon cancer.

Two or more asynchronous polyps of the colon. There were 15 cases in this group. Eight patients underwent 2 successive operations for removal of polyps, 3 had 3 operations, 3 had 4, and 1 had 5. Three died of unrelated causes and 12 are living and well. All 15 have been followed for an average period of 8½ years to an average age of 66 years. Three of these patients subsequently were found to have a cancer of the colon which was resected. They are well 2, 4, and 5½ years since operation at an age of 51, 84, and 86 years respectively. None would have benefited so far from the radical type of operation.

Thus in these 6 groups of patients with multiple polyps, with and without coexisting cancers, only 1 out of 67 might have been helped by subtotal or total colectomy. In 6 patients, a cancer of the colon was found and resected subsequently which would have been avoided if a radical colectomy had been done initially. Only 1 of these patients, however, died of cancer. The remaining 5 have continued well for an average period of 4½ years since the removal of the tumor at an average age of 74 years.

The average diameter of the polyps in these 6 groups was 1.5 centimeters.

CANCER OF THE COLON

Subtotal and total colectomy has also been proposed for patients with cancer of the colon in the hope of preventing other subsequent primary cancers. Accordingly, our experience with multiple cancers of the colon was reviewed. In a total of 1,753 resections from 1916 to 1952 inclusive, multiple cancers of the colon and rectum were found at this hospital in 89 patients, an incidence of 5.1 per cent. In 1,083 resections in the colon alone, multiple cancers were found in 63 patients, an incidence of 5.8 per cent. In an incomplete review since 1952 of patients undergoing colon resection, 11 more with multiple cancers of the colon and rectum with at least a 3 year follow-up have been found, making a total of 100 patients. Fifty-eight of the patients (58 per cent) had synchronous cancers, in that they were all discovered at one time, and 42 (42 per cent) were asynchronous in that they were found and treated consecutively at subsequent intervals. Twenty-five of the patients with synchronous cancers had cancers involving the rectum which were therefore excluded, leaving 33 patients with synchronous colon cancers in which subtotal or total colectomy might have been done. However, these patients would not have been helped by these procedures since they did not have subsequent cancers as the term synchronous implies, although of course this was not known when they were first seen. Of the 42 patients with asynchronous cancers, 21 had cancers involving the colon only and were also suitable for the radical procedure. Of the remaining 21 patients with asynchronous cancers, 7 had cancers involving the rectum when first seen and would therefore not have been considered for this procedure, whereas 12 patients had cancers involving the rectum subsequently. The radical operation might well have been done on these patients when first seen although it would not have prevented the subsequent rectal

cancers. There were 2 other cases in which only palliative treatment would have been possible.

As shown in Table I there were thus 66 patients with multiple cancers in which subtotal or total colectomy might have been attempted. Thirty-three had synchronous colon cancers, 21 had asynchronous colon cancers and 12 had a colon cancer at the first operation and a rectal cancer subsequently. Obviously, any favorable result would have to come from the second group. In all 66 patients, the average length of follow-up of those still living and well was 10 years and the average age at the end of the follow-up period was 68.6 years.

In reviewing the histories of the 21 patients with asynchronous colon cancers, 8 were found who might have benefited from the operation had it been done. Five of these died from subsequent colon cancers, 2 from complications accompanying the second operation and 3 from the disease itself. In 2 other cases it was difficult to determine whether the recurrence came from the first or the second cancer. In another case it was uncertain whether the second cancer was a new primary tumor or a suture line recurrence. These cases were included however.

Thus 8 patients might have benefited out of 66 on whom the operation might have been attempted. All 8 cases occurred in the 1916 to 1952 period during which 1,083 cancers of the colon were resected. Had subtotal or total colectomy been done in all these cases, the 8 cases would represent a possible salvage of only 0.73 per cent of the whole group. This figure represents only about one-sixth of the possible operative mortality alone, without bringing up any question of cure.

TABLE I.—PATIENTS WITH MULTIPLE CANCERS OF COLON AND RECTUM (1916 TO 1953 INCLUSIVE)

	No.
Synchronous cancers (colon only)	33
*Synchronous cancers (at least one cancer in rectum)	25
Asynchronous cancers (colon only)	21
*Asynchronous cancers (rectal cancer on first admission)	7
Asynchronous cancers (colon cancer on first admission and rectal cancer subsequently)	12
*Asynchronous cancers (palliative treatment only)	2
Total	100

*Unsuitable for subtotal or total colectomy.

DISCUSSION

In reviewing the histories of patients with multiple polyps and multiple cancers, it was surprising to find how well most of them have done when treated by conventional methods for removal of polyps and with segmental resection of the cancers, even when repeated operations were necessary. Of course, the success of this treatment depends largely on how frequently patients are seen in the follow-up clinic, how carefully they are questioned and examined, how long the follow-up is maintained, and how often proctoscopic and x-ray examinations are carried out. In hospitals and areas where adequate follow-up facilities are not available the results should not be as good. Very few of our patients developed subsequent cancers during the period that they were followed which were not recognized and treated in time. The 46 patients with multiple polyps who have remained alive and apparently well were observed for an average of 8.2 years after operation and to an average age of 63.6 years. The 23 patients with multiple cancers who have been alive and well have been followed for an average of 10 years and to an average age of 68.6 years. Of course it is possible that a new colon cancer may still arise in these patients that could have been avoided by early subtotal or total colectomy but this possibility seems unlikely as most of these patients are close to the end of their life expectancy.

CONCLUSIONS

1. From the follow-up results in 6 types of cases with multiple polyps of the colon in which subtotal or total colectomy might have seemed advisable, only 1 patient out of 67 could have benefited.

2. From the follow-up results in 66 patients with multiple cancers of the colon in which subtotal or total colectomy might

have seemed indicated, only 8 could have benefited from the operation. This number represents a possible salvage of only 0.73 per cent of the 1,083 cancers resected during that period.

3. From this study the treatment of patients with cancer and multiple polyps of the colon by subtotal or total colectomy does not appear to be justified or advisable except perhaps in a few selected cases.

REFERENCES

1. Deddish, M. R., and Hertz, R. Colotomy and coloscopy in management of mucosal polyps and carcinoma of the colon. Am. J. Surg., 1955, 90: 846-849.
2. Grinnell, R. S., and Lane, N. Benign and malignant adenomatous polyps and papillary adenomas of the colon and rectum; an analysis of 1856 tumors in 1335 patients. Surg. Gyn. Obst., Internat. Abstr. Surg., in press.
3. Lillehei, R. C., and Wangensteen, O. H. Bowel function following colectomy for cancer, polyps, and diverticulitis. J. Am. M. Ass., 1955, 159: 163-170.
4. McLanahan, S., and Martin, R. E. Colotomy, coloscopy, and colectomy in the management of polyps of the large intestine. Ann. Surg., 1957, 145: 689-698.
5. Public Health Monograph No. 29.
6. Scarborough, R. A. Discussion of papers of American Proctologic Society. Am. J. Surg., 1955, 90: 856-857.
7. Teicher, I., and Abrahams, J. The treatment of cases of multiple polyps, familial polyposis, and diverticular disease of the colon by subtotal colectomy and ileoproctostomy. Surg. Gyn. Obst., 1956, 103: 136-146.

THE TREATMENT OF THROMBOEMBOLISM WITH AQUEOUS HEPARIN

HAROLD W. HARROWER, M.D., Providence, Rhode Island,
ALFRED HURWITZ, M.D., Brooklyn, New York, and
RAYMOND YESNER, M.D., West Haven, Connecticut

MANY INVESTIGATORS consider heparin the best anticoagulant available today. It is more effective than dicumarol in the prevention and treatment of experimental thrombosis, and in most patients its action is more predictable than that of dicumarol. Heparin rarely causes spontaneous hemorrhage, and it can be used in some patients with hepatic or renal disease in whom dicumarol is contraindicated.

Despite the extensive use of heparin since its discovery by McLean in 1916, there is no general agreement on optimal dosage or route of administration. The intermittent intravenous injection of heparin has been the most widely used method of treatment. Heparin has also been administered by continuous intravenous injection. The intramuscular or subcutaneous injection of sufficient amounts of heparin at regular intervals produces prolonged or continuous clotting time elevations. Aqueous heparin injected intramuscularly is absorbed at a slightly faster rate than when given subcutaneously. Heparin administered intramuscularly is too painful and too frequently associated with hemorrhages at the site of injection to justify its clinical use. Concentrated aqueous heparin injected subcutaneously in the same amounts as depo-heparin preparations produces clotting time responses that are similar in degree and duration, and the use of these latter preparations seems to have no advantage.

Our experience with subcutaneously administered concentrated aqueous heparin therapy confirmed many of the findings of other workers, but revealed certain difficulties and hazards which deserve emphasis. In the group of patients to be discussed, blood viscosity studies proved a valuable addition to clotting time determinations.

From the Surgical and Pathology Services of the Veterans Administration Hospitals, Newington and West Haven, Connecticut.

METHODS OF STUDY

Two preparations of concentrated aqueous heparin (as the sodium salt) were employed for all subcutaneous injections. Both preparations are commercially available, and contain respectively, 100 and 200 milligrams of heparin per cubic centimeter.

For intravenous administration, a preparation containing 10 milligrams of heparin per cubic centimeter or one of the more concentrated solutions diluted to this concentration was used. For subcutaneous administration, No. 25 or 26 hypodermic needles and 1 or 2 cubic centimeter tuberculin syringes were used. Nursing and medical personnel were instructed in the technique of giving deep subcutaneous injections.

Blood specimens were withdrawn from arm veins. A single, clean puncture through dry, prepared skin was mandatory. One to 2 cubic centimeters more blood than were required for testing were obtained so that the 1 to 2 cubic centimeters of blood which had been withdrawn first could be discarded. If more than 2 minutes were required to transport the blood specimen to the laboratory, and, in all instances in which viscosimeter studies were done, siliconized needles and syringes were used. When a clotting time alone was required, nonsiliconized equipment was used if the test could be done

TABLE I.—INDICATIONS FOR HEPARIN THERAPY

	No. of patients					
	Postoperative			Nonoperative		
Diagnosis	*q.6 h. schedule*	*q.12 h. schedule*	*Total*	*q.6 h. schedule*	*q.12 h. schedule*	*Total*
Thrombophlebitis	7	20	27	9	13	22
Thrombophlebitis and pulmonary embolism	1	7	8	2	5	7
Pulmonary embolism without evidence of thrombophlebitis	2	1	3	2	0	2
Other	0	1*	1	3†	2‡	5
Total	10	29	39	16	20	36

*Coronary artery thrombosis in O.R. while undergoing herniorrhaphy.
†(1) Axillary vein thrombosis following weight lifting.
(2) Thrombosis of central retinal artery, spontaneous.
(3) Raynaud's syndrome, upper extremity.
‡(1) Embolic occlusion central retinal artery, left, from mural thrombus in left auricle; chronic rheumatic heart disease.
(2) Acute myocardial infarction 1 month after compression fracture of L_2 and multiple rib fractures; prophylactic.

within 2 minutes after venipuncture.

For blood collected in siliconized syringes, clotting time and viscosimeter studies were timed from the moment of transfer of the specimens to clotting or viscosimeter tubes. For blood collected in nontreated syringes, zero time was taken as the time of venipuncture. Blood viscosity changes were studied by means of an electronic instrument which measures instantly and records graphically the changing viscosity of blood. The use of this instrument has been reported previously (4, 6). Viscosimeter studies were performed with specimens at 37 degrees C. Some blood specimens were examined by a recalcification technique (5).

Clotting times were done by a modified Lee-White method using 2 nonsiliconized tubes (13 by 100 mm.) rinsed with physiologic saline and incubated at 37 degrees C.; 1.0 cubic centimeter of blood was introduced into each of 2 coagulation tubes. After a 3 minute interval the first tube was tilted every minute until clotting occurred. The second tube was then tilted every minute. The end point was taken as the time at which no blood flow occurred on tilting to 180 degrees. The time in minutes from the beginning of the test to the end point in the second tube was recorded as the clotting time. Normal values are 5 to 10 minutes.

Early in this study, heparin therapy was directed by the authors, and clotting times and viscosity curves were obtained at frequent intervals. Later on, therapy was directed by the clinical personnel responsible for each patient, and clotting times alone were followed routinely. On the 6 hour heparin schedule, clotting times were done between 5 and 6 hours after at least 2 injections during a 24 hour period. On the 12 hour schedule, clotting times were performed 6 and 11 hours after each injection. On either schedule, clotting times were performed less frequently after a maintenance dose was established. As a rough guide, the range of clotting times desired was considered to be between 15 and 50 minutes.

CLINICAL MATERIAL

Fifteen healthy adults were given concentrated aqueous heparin (200 mgm. per c.c.) subcutaneously, and the effects were followed by clotting time determinations. There were 3 female and 12 male subjects. They varied in weight from 110 to 220 pounds, average 167 pounds. The age range was 22 to 43 years, average 31 years. All subjects received an initial injection of 1.5 milligrams of heparin per pound of body weight. The amounts of heparin injected varied from 165 milligrams for the lightest subject, C—110 pounds, to 330 milligrams for the heaviest subject, D—220 pounds. Ten subjects received a second injection 12 hours after the first; this dosage varied from 0.8 to 1.5 milligrams of heparin per pound.

Seventy-five patients received a total of 86 courses of subcutaneous heparin; 8 patients received more than one course. Heparin was administered to 26 patients on a 6 hour schedule, and to 49 patients on a 12 hour schedule. The average age of the patients was 44 years. The youngest patient was 22 and the oldest 72 years old. Weight varied from 125 to 250 pounds, average 170. Except for 1 negro male, and 1 white female, all patients were white males.

The indications for heparin therapy are listed in Table I. In the tables, the term

thrombophlebitis includes phlebothrombosis. Except as noted, all thromboses occurred in the lower extremities. In 39 patients (52 per cent) the thrombotic disorder followed operation, and in 36 patients (48 per cent) it was not associated with any surgical procedure. Sixty-four patients had phlebothrombosis or thrombophlebitis, and in 15 of these patients one or more episodes of pulmonary embolism occurred prior to treatment. Five patients had pulmonary embolism without evidence of venous thrombosis anywhere. Six patients had other thrombotic disorders.

In the 39 patients who developed postoperative thromboembolic complications, the following pertinent conditions existed; 6 patients had visceral carcinoma; 1, a benign tumor of the chest wall; 2, diverticulitis of the colon; 2, recent trauma; and 6, a history or preoperative findings indicative of previous deep venous thrombosis of the lower extremities. The operations were major in 33, and minor in 6 instances, and included general surgical, thoracic, orthopedic, and urologic procedures.

In 12 of the 36 patients who developed a thromboembolic condition not related to an operative procedure, this represented an initial, apparently spontaneous condition. Nine patients gave a history of previous episodes, or showed evidence of chronic deep venous obstruction of the lower limbs. Three patients had malignant disease, 2 visceral carcinoma and 1 leukemia. Four patients had heart disease. Infection was a factor in 3 patients; chronic suppurative lung disease in 1, cellulitis of the leg in the second, and recurrent osteomyelitis of the leg in the third patient. Recent trauma had occurred in 1 patient. Thromboangiitis obliterans, idiopathic recurrent migrating phlebitis, Raynaud's syndrome, and postpoliomyelitis paraplegia were diagnoses established in 4 other patients in the nonoperative group.

Prior to the institution of subcutaneous heparin therapy, in 39 instances there was no anticoagulant treatment, in 40 instances one or more intravenous injections of heparin were given at 4 hour intervals, in 3 instances dicumarol therapy was used, and in 4 instances vein ligations had been performed. Of the 40 instances in which intravenous heparin was employed, this therapy was used for less than 24 hours in 22, from 2 to 11 days in 15, and for more than 11 days in 3 instances.

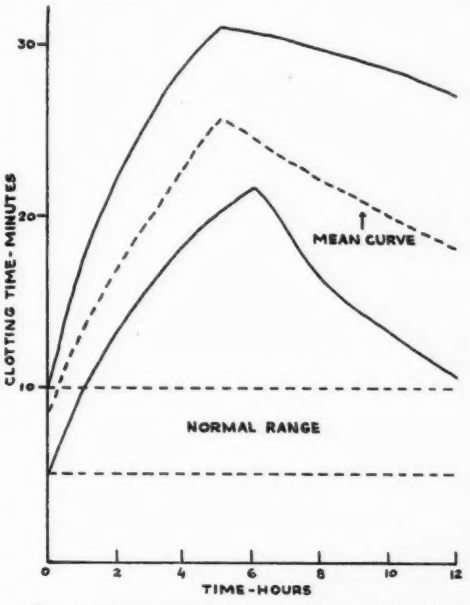


FIG. 1. Clotting time response of 15 normal subjects following the subcutaneous injection of concentrated aqueous heparin (1.5 mgm. per pound of body weight). Solid lines represent the range.

RESULTS

In the group of healthy volunteers, preheparin clotting times ranged from 5 to 10 minutes (average 7.6). Following the subcutaneous injection of 1.5 milligrams of heparin per pound of body weight, an appreciable increase in clotting time was present 1 hour after injection; between 4 and 6 hours, clotting times were 2½ to 5 (average 3.4) times preinjection levels; and at 11 to 12 hours, clotting times were 1½ to 3 (average 2.4) times preinjection levels (Fig. 1). In the 10 subjects who received a second injection

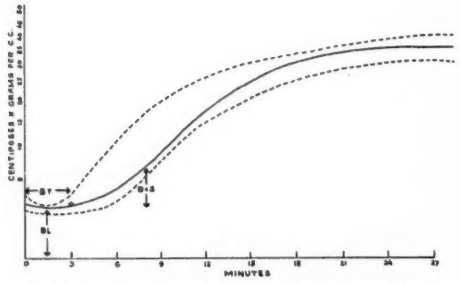


FIG. 2. Blood viscosity profiles of 21 normal subjects—mean curve and range. The height, *BL*, of the initial plateau averages 1.9 centipoises, and the latent period, *BT*, has an average duration of 3 minutes and 10 seconds. *B+5* designates the increase in viscosity which occurs in the 5 minute interval following the beginning of the rise of the main curve (marked by an arrow).

of heparin, clotting times 11 to 12 hours after injection varied from 1½ to 4 times control values depending upon the response to the first injection and the amount of heparin used. These results are similar to those obtained by Artz and associates (1, 2) and by Engelberg. The clotting time responses of different subjects varied over a fairly wide range despite the use of weight-equivalent doses of heparin (Fig. 1).

An average blood viscosity curve constructed from the curves of 21 normal individuals is shown in Figure 2. There is an immediate rise, and after a short period of equilibration, a drop back to a lower plateau, and then a main rise which levels off after a variable length of time. The vertical scale is in viscosity units, centipoises, and the horizontal scale is in minutes. The arrow indicates the point on the plateau at which the main rise begins. The height of the plateau, *BL*, averages 1.9 centipoises. The time elapsing from the start of the curve to the start of the main rise, *BT*, represents a latent period and averages 3 minutes and 10 seconds. There is no change on the curve to indicate where clotting occurs.

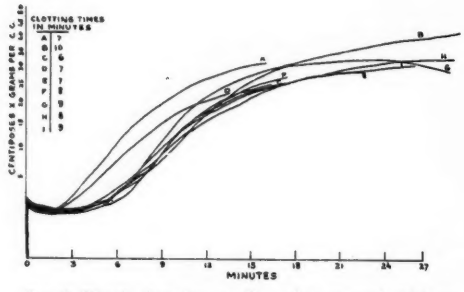


FIG. 3. Blood viscosity profiles of 9 normal subjects prior to heparin administration.

The viscosity curves of 9 normal subjects before and after the injection of subcutaneous heparin are shown in Figures 3 through 6. Four to 6 hours after injection, there is marked flattening of the curves for all subjects except D (Fig. 4). Clotting times range from 21 to 29 minutes. Subject D, whose curve is only moderately flattened, has a clotting time of 29 minutes. At 11 to 12 hours postinjection, the curves have risen slightly (Fig. 5), but are still flattened as compared with the preinjection curves. Clotting times range from 12 to 28 minutes. The curve of subject D is an exception, having returned to its original shape, although the clotting time is 20 minutes. Seven of the 10 subjects who received a second injection of subcutaneous heparin were followed with blood viscosity profiles (Fig. 6). At 11 to 12 hours postinjection, the curves of subjects A, B, and D have returned to their preheparin levels, although the clotting time of subject B remains elevated (21 minutes). The curves of subjects C, F, G, and I remain flattened with clotting times varying from 10 to 35 minutes.

In normal subjects, the changes in blood viscosity profiles following subcutaneous heparin injections were similar to those produced by intravenous heparin but of longer duration. As with intravenous heparin the degree and duration of alteration of the viscosity profiles tended to, but did not always, parallel corresponding changes in the clotting times.

In patients, pretreatment clotting times varied from 3 to 11.5 minutes (average 7.0 minutes). Four of the 8 patients whose clotting times were under 5 minutes showed other evidence of hypercoagulability. The 1 patient with a clotting time of over 10 min-

utes proved sensitive to heparin, had a low blood viscosity profile, and bled on therapy.

On the 6 hour schedule, only 4 of 8 patients who received initial doses of less than 1.0 milligram of heparin per pound had a satisfactory response. Seven of 11 patients who were given 1.0 to 1.4 milligrams of heparin per pound and all 8 patients who were given 1.5 or more milligrams per pound attained satisfactory clotting times.

On the 12 hour schedule, 3 patients were given initial injections of less than 1.0 milligram of heparin per pound and did not have satisfactory clotting times. Five of 10 patients who received 1.0 to 1.4 milligrams of heparin per pound and 31 of 42 patients who received 1.5 or more milligrams of heparin per pound did attain satisfactory clotting time elevations. In 14 instances in which the clotting time response to the first dose was satisfactory, heparin in doses ranging from 30 to 75 milligrams had been administered intravenously at the same time as, or just prior to the subcutaneous injection. Three of the patients with unsatisfactory clotting time responses had received complementary heparin intravenously.

The amount of the second dose of heparin was gauged from the response to the first. In 63 patients, sufficient data were available to evaluate the clotting time response to both injections. Of 16 patients on the 6 hour schedule, 12 had satisfactory clotting times after the second injection. Eleven of these 12 patients had had satisfactory clotting times after the first dose of heparin and received less than 1.0 milligram of heparin per pound for the second dose. Thirty-one of 47 patients on the 12 hour schedule had satisfactory clotting times following the second heparin injection. Of these 31 patients, 2 received less than 1.0 milligram; 24, 1.0 to 1.4 milligrams; and 5, 1.5 or more milligrams of heparin per pound. Twenty patients had had satisfactory, and 11 patients unsatisfactory clotting time responses after the first injection. The net result of the first 2 doses of heparin was the attainment of satisfactory clotting times by the end of the second injection period in about two-thirds of the cases.

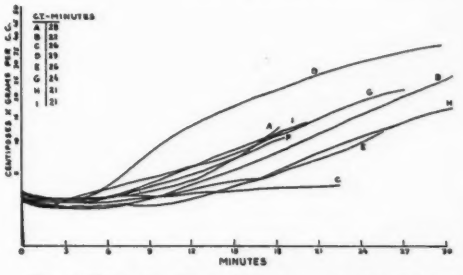


FIG. 4. Blood viscosity profiles of normal subjects 4 to 6 hours after the subcutaneous injection of concentrated aqueous heparin (1.5 mgm. per pound of body weight).

The establishment of a maintenance dosage of subcutaneous heparin proved to be a matter of trial and error. In many instances in which the first 2 injections produced satisfactory responses, stability of dosage was readily achieved. In some patients, progressively increasing amounts of heparin were needed. Frequently, after 3 to 7 days of therapy, there appeared an increased responsiveness to heparin which necessitated a sharp reduction in dosage. In the majority of patients, after this period of instability, heparin dosage was very constant for days or weeks. In terms of total daily heparin dosage, most patients required between 300 and 400 milligrams. Some patients required considerably larger amounts. Two patients received more than 800 milligrams of heparin per day for more than 48 hours without

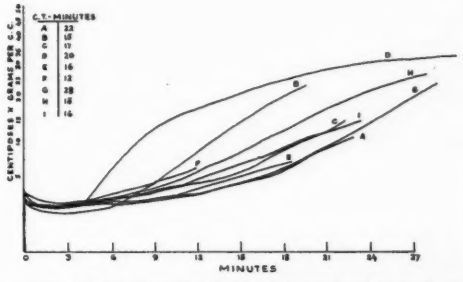


FIG. 5. Blood viscosity profiles of normal subjects 11 to 12 hours after the subcutaneous injection of concentrated aqueous heparin (1.5 mgm. per pound of body weight).

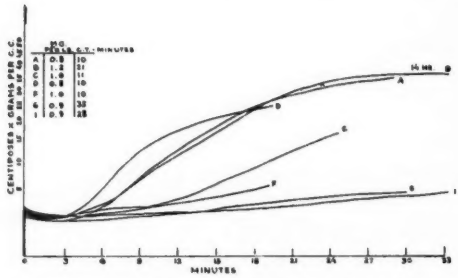


FIG. 6. Blood viscosity profiles of normal subjects 11 hours after a second subcutaneous injection of concentrated aqueous heparin (1.5 mgm. per pound of body weight).

having excessive clotting times. Both patients had sustained pulmonary emboli, and 1 patient had a retrograde thrombophlebitis which occurred following ligation of the inferior vena cava.

In patients with acute thromboembolic conditions when clotting times were below satisfactory levels, additional heparin (30 to 75 mgm.) was given intravenously to provide an effect until the subcutaneous dosage could be adjusted. Ambulation appeared to produce slightly faster absorption of subcutaneous heparin. This phenomenon was more apparent on the 12 hour schedule.

In 18 courses of heparin administered on a 6 hour schedule, a stable maintenance dose was established. This dose varied from 0.6 to 1.1 milligrams per pound, average 0.75. In 10 courses of treatment heparin dosage was unstable throughout. In 3 courses heparin was not given long enough to determine a maintenance level. On the 12 hour schedule of heparin administration, a stable maintenance dose was achieved in 46 courses and ranged from 0.8 to 1.5 milligrams per pound, average 1.2. Maintenance dosage was very unstable in 5 courses and not determined in 4 courses. Stability of heparin dosage was more difficult to establish on the 6 hour than on the 12 hour schedule, and cumulative effects occurred more frequently.

The 200 milligram per cubic centimeter heparin seemed to be absorbed at a slightly slower rate than the 100 milligram per cubic centimeter heparin. This difference appeared to be of little clinical importance and in many patients, one preparation of heparin was substituted for the other without significant differences in clotting times.

Pretreatment viscosity profiles were obtained on 21 patients. Some of these are shown in Figure 7. Eleven (52.4 per cent) of the profiles showed a precipitous rise of the main curve, and all of these patients had a moderate to marked resistance to heparin, as measured by both clotting time and viscosity curve responses. In many patients, there was noted, in addition to a rapid rise in the main curve, a shortening of the latent period. The changes in viscosity profiles produced by subcutaneous heparin were similar to those observed in normal subjects.

The effect of heparin on the viscosity profile was usually proportional to its effect on the clotting time. Discrepancies, however, occurred fairly often, especially in the early phases of treatment in patients who were resistant to therapy. Viscosity profiles frequently seemed to reflect changes in heparin requirements sooner than did clotting times (Fig. 6). The association of a satisfactorily prolonged clotting time with a high main viscosity curve usually presaged a need for an increase in heparin dosage. This combination of findings generally occurred in the first few days of treatment, and when the same doses of heparin were continued, there was subsequent failure of satisfactory clotting time response, and, in some instances, a higher viscosity curve than previously observed in that patient. Conversely, when viscosity curves were flattened out of proportion to clotting times, continued injection of the same amounts of heparin often produced excessive responses. On the 12 hour schedule, a significant anticoagulant effect was often apparent on the viscosity profile 11 to 12 hours after injection, although the clotting time had returned to the normal range.

For patients with thromboembolic conditions body weight was a helpful but not reliable guide to heparin dosage. There was a

great deal of variation in the clotting time responses of patients given weight-equivalent amounts of heparin, and in individual patients there was frequently considerable variation in heparin requirements from day to day and even from one dose to another. From the point of view of clotting time control as defined in this study, subcutaneous heparin therapy was satisfactory in about two-thirds of the courses. The supplementary use of intravenous heparin was helpful in assuring immediate anticoagulant effects.

Sixty-five patients with thromboembolic disorders were given definitive anticoagulant treatment (Table II). Thirteen patients received 14 courses of combined subcutaneous heparin and dicumarol. The start of dicumarol varied from the first to the fourteenth day (average sixth day) of treatment. The duration of heparin therapy ranged from 3 to 22½ days, average 9.7. Heparin was usually discontinued when the prothrombin level (one stage method of Quick) was below 30 per cent on 2 successive days.

In 4 courses of combined therapy the transition from heparin to dicumarol was accomplished smoothly. In the other 10 courses there appeared varying degrees of hyperresponsiveness to heparin as the dicumarol-induced hypoprothrombinemia increased. This sensitivity usually became apparent when the prothrombin time fell below 40 per cent. In 3 instances, there occurred suddenly excessive clotting times in response to amounts of heparin which had previously produced satisfactory levels. In 6 instances in which the development of hypoprothrombinemia was gradual, heparin doses were progressively reduced one-third to one-half with maintenance of the same range of clotting time prolongations.

When subcutaneous heparin and dicumarol are administered concomitantly, the laboratory determinations used for the control of each drug tend to be inaccurate. With intermittent intravenous administration, this tendency is not an insuperable problem, if blood for the prothrombin test is drawn at a time when the effects of the last

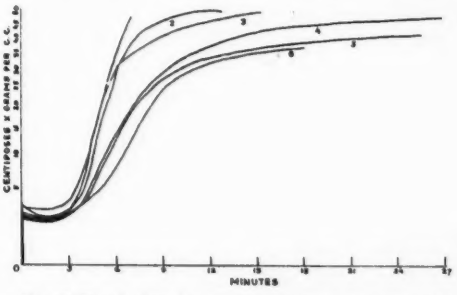


FIG. 7. Blood viscosity profiles of some patients with thromboembolic disease prior to anticoagulant therapy.

heparin injection have been dissipated. With the continuous effects of subcutaneous heparin this is not possible. These difficulties are further compounded by the fact that the action of heparin is potentiated by dicumarol-produced hypoprothrombinemia.

Eleven of the 13 patients treated with heparin and dicumarol showed regression of their thromboembolic disorders and made uncomplicated recoveries. In 2 patients, thromboses progressed and pulmonary emboli occurred on presumably adequate dicumarol therapy, after heparin was discontinued. Both patients underwent proximal vein ligations and subsequently developed retrograde thrombophlebitis which eventually subsided on subcutaneous heparin therapy. One other patient, a young man with a florid, superficial thrombophlebitis of both calves, responded dramatically to subcutaneous heparin therapy after having failed to improve on a 3 week period of well controlled dicumarol treatment.

Subcutaneous heparin was administered, as the sole anticoagulant, to 52 patients with thromboembolic disorders. These patients

TABLE II.—DURATION OF DEFINITIVE ANTICOAGULANT THERAPY

	Subcutaneous heparin alone				*Subcutaneous heparin with or prior to dicumarol*			
Schedule	*No. of patients*	*No. of courses*	*Range, days*	*Average, days*	*No. of patients*	*No. of courses heparin*	*Range, days*	*Average, days*
q.6 h.	15	18	2–30	11.6	3	3	5¼–11	9
q.12 h.	37	41	2–50	12.0	10	11	3–22½	10.4
Total	52	59	2–50	11.8	13	14	3–22½	9.7

TABLE III.—RESULTS OF DEFINITIVE SUBCUTANEOUS HEPARIN THERAPY

Relation of thromboembolism to operation	*Satisfactory*	*Unsatisfactory*	*Therapy too short to evaluate*
Nonoperative	21	0	0
Postoperative	23	3	5
Total	44	3	5

6 and 12 hour schedules combined.

received heparin for periods of 2 to 50 days, average 11.8. In 5 patients subcutaneous heparin was discontinued after 2 to 4 days because of complications. In the remaining 47 patients, the results of therapy were evaluated (Table III). The thromboembolic conditions treated occurred following operation in 25 patients, and were not related to any surgical procedure in 22 patients. Pulmonary emboli had occurred in 13 patients. In 44 patients (93.6 per cent), subcutaneous heparin therapy was satisfactory in terms of subsidence of thrombophlebitic processes and the absence of pulmonary emboli. Subcutaneous heparin therapy produced in almost all patients early and striking relief of pain and regression of local inflammatory reactions. Thrombophlebitis recurred or pulmonary emboli occurred during, or following subcutaneous heparin treatment in 3 patients. One patient had a fatal embolus on therapy.

No sensitivity reactions to subcutaneous heparin were encountered. Except for 1 patient who consistently developed painful nodules, untoward pain at injection sites was usually associated with hematoma formation which occurred in about 2 per cent of injections and was minimal with the 200 milligram per cubic centimeter preparation. Injections of more than 1.5 cubic centimeters of heparin solution were especially apt to cause local hemorrhage.

Most patients who had hemoptysis following a pulmonary embolus continued to have hemoptysis on subcutaneous heparin therapy. In some patients hemoptysis occurred for the first time after the start of therapy and was considered a confirmatory sign of pulmonary embolization. Hemoptysis did not become troublesome or alarming.

Of the 75 patients who received subcutaneous heparin 3 developed major hematomas at sites of injection. One patient was on a 6 hour treatment schedule and the other 2 were on a 12 hour schedule. The hematomas were subcutaneous in 1 and subfascial in 2 patients. Of the 2 subfascial hemorrhages, one was attributed to the administration of heparin intramuscularly rather than subcutaneously and the other to the trauma of intramuscular penicillin injections. Hemorrhages occurred on the sixth, ninth, and twelfth days of therapy, respectively. On the day of hemorrhage clotting times ranged between 20 and 45 minutes in all 3 patients. All of the hematomas resolved despite the continuation of heparin therapy, subcutaneously in 1, and intravenously in 2 patients.

Bleeding into or from operative wounds occurred in 7 patients. The wounds involved were anorectal in 3 patients, tooth socket in 1[1], incision for inguinal hernirrhapy in 1, incision for femoral vein ligation in 1, and arthrotomy (knee) incision in 1. Three patients were on a 6 hour, and 4 on a 12 hour schedule. Bleeding occurred on the second, fifth, seventh (2 patients), eighth, and ninth (2 patients) postoperative days, and on the second (2 patients), third (2 patients), fourth, fifth, and sixth days of subcutaneous heparin therapy, respectively. At the time of hemorrhage, and for the preceding 12 hour period, clotting times were within the "therapeutic range" in 4 patients, and exceeded this range in 3 patients. Peak clotting times for these latter patients were 55, 75, and 90 minutes, respectively. Bleeding was major in 4, and minor in 3 patients. Protamine sulfate was administered intravenously to 5 patients to counteract the action of heparin. In all instances clotting times were promptly restored to normal levels. Heparin therapy was not resumed in 3 patients. In 4 patients, after bleeding was controlled, intermittent intravenous heparin

[1]This patient had a tooth extraction 6 days following subtotal gastrectomy. Seven days following gastrectomy he was given heparin therapy because of thrombophlebitis of one lower extremity.

therapy was instituted without additional hemorrhagic complications.

Although clotting times were excessive in only 3 patients, 6 of the 7 patients who developed wound hemorrhages did so in a phase of increasing sensitivity to heparin. Blood viscosity profiles were obtained in 3 of these 6 patients following the occurrence of bleeding. In 2 instances, the viscosity profiles were flattened out of proportion to the clotting times, which were 25 and 30 minutes, respectively.

Bleeding other than at sites of injection or operative wounds occurred in 4 patients on subcutaneous heparin therapy. Two patients had minor epistaxes on the thirteenth and fourteenth days of treatment, respectively. Both patients were on a 12 hour schedule, clotting times were not excessive in either patient, and heparin therapy was continued without further bleeding. One patient on a 6 hour schedule had nosebleeds on the fifth and seventh days of therapy. On both occasions, peak clotting times were under 30 minutes, bleeding stopped spontaneously, and heparin therapy was continued uneventfully. The fourth patient had chronic myelogenous leukemia, thrombophlebitis of both lower extremities, and multiple pulmonary infarcts. He was treated on a 6 hour schedule, and during the second week of treatment had repeated epistaxes. At that time he had become very responsive to heparin, but thrombocytopenia was also present. Anticoagulant therapy was stopped. Nosebleeds, however, continued to occur and purpura developed.

Ten patients other than those discussed had, during subcutaneous heparin treatment, excessively prolonged clotting times (up to 180 minutes in 1 patient) over periods of time ranging from 4 to 24 hours. None of these patients developed clinical bleeding, although in 5 patients the risk of hemorrhage was relatively high because of recent major operative procedures. Two of these 5 patients had large, raw surface areas which had been denuded as a result of tumor excisions.

DISCUSSION AND CONCLUSIONS

It has not been determined whether frequent intermittent elevations of the clotting time, as with intravenous heparin, or sustained elevations, as with subcutaneous heparin, are more effective in the therapy of thromboembolic conditions. Clinical experience and animal experiments suggest that adequate anticoagulant effects are present when the clotting time is prolonged to 2 or 3 times normal levels.

A reasonable goal of subcutaneous heparin therapy would appear to be to maintain clotting times at such levels by the injection of standard amounts of heparin at regular time intervals. Concentrated aqueous heparin administered every 12 hours in amounts of 100 to 200 milligrams (some allowance being made for body weight) had been reported to attain this objective almost uniformly.

With respect to control of clotting time our results with subcutaneous concentrated aqueous heparin therapy have been less gratifying. Heparin requirements varied so widely among our patients and in the same patient from time to time that the use of any fixed dosage would have resulted in the overheparinization or underheparinization of a considerably larger number of patients than was the case when dosage was individualized according to the clotting time response.

In patients who were refractory to heparin, or in whom heparin requirements were changing rapidly, the slow absorption of concentrated aqueous heparin delayed the discovery and correction of these conditions. In some patients, blood viscosity profiles after insufficient amounts of heparin, indicated a greater degree of abnormality than was present prior to treatment.

We found, as others have, that especially in patients with acute thrombotic conditions or pulmonary emboli initial heparin requirements may far exceed conventional doses. In such patients heparin requirements frequently decrease after 3 to 7 days of therapy, and this increased responsive-

ness to heparin is often accompanied by clinical improvement of the thromboembolic process. In some instances, changes in responsiveness to heparin were quite abrupt, and prompt reduction of dosage was necessary. All except 1 of our hemorrhagic wound complications took place during this phase of treatment, although clotting times were excessive in only 3 patients. Once this period of instability was passed, most patients were easily managed.

There are no tests which will consistently predict the occurrence of venous thrombosis or even indicate its presence. Although the peripheral blood of patients with thromboembolism is hypercoagulable in many instances, blood coagulability may be normal or even decreased. Heparin tolerance tests have shown similar findings; many patients are hyporeactors, some are normoreactors, and a few are hyperreactors. Hypercoagulability and heparin resistance occur in many conditions. The interpretation of alterations in blood coagulability or heparin tolerance is further complicated by the fact that these changes are not static and linear but dynamic and polyphasic.

The effect of heparin on the clotting time appears to depend on its concentration in the blood rather than on the method of administration, but there is considerable variation in the response of the clotting time to any one concentration of heparin in different patients. No matter how injected, heavy subjects need more heparin than light subjects to produce similar clotting time elevations, and the larger the amount of heparin used the higher the clotting time peak and the longer the duration of effect. It has been our experience and that of others that in any 1 patient once heparin dosage is stabilized, daily heparin requirements are approximately the same regardless of the route of administration.

Whenever subcutaneous heparin does not produce the expected effect on the clotting time, the response to intravenous heparin should be tested to rule out local inactivation or a defect in absorption. In this series all patients tested who were resistant to subcutaneous heparin were similarly resistant to intravenous heparin.

Blood viscosity may be altered by many different conditions. These alterations are not specific, and the mechanisms by which they are brought about have not been elucidated. In any event, viscosity profiles were found to be a useful and informative indicator of changes in blood coagulability in patients with thromboembolism. We cannot draw any definite conclusions regarding the use of viscosity profiles in controlling heparin therapy because clotting times were used for that purpose. In studies of experimental venous thrombosis in dogs, significant alterations of blood viscosity profiles were found in animals with thrombosis compared with control animals. Blood viscosity profiles would seem to have some advantages over other tests that measure changes in blood coagulability in that a graphic record is obtained, as many as 6 specimens can be examined simultaneously, and the tests can be run sometime after the blood specimens are drawn.

The Lee-White clotting time determination is a poor indicator of pretreatment alterations in the coagulability of the blood of patients with thromboembolic conditions (only 9 of our 75 patients had abnormal values). Changes in the clotting time produced by heparin therapy reflect but one facet, and possibly not the most important, of the anticoagulant action of heparin. Clotting time tests remain, however, a practical method for following heparin therapy, and regardless of the route of administration should be performed frequently enough to permit adequate regulation of dosage.

Our clinical results confirm the conclusions of other workers that concentrated aqueous heparin administered subcutaneously is, for the most part, an effective method of therapy. Subsidence of the pain and of the local inflammatory signs of acute thrombotic processes appears to be as rapid and complete as when heparin is employed intravenously. After heparin requirements

have become stable, subcutaneous heparin therapy can be continued in most patients for prolonged periods of time with only occasional clotting time checks. It provides greater comfort to patients and less inconvenience for the doctor than is possible with other routes of administration.

On the basis of our experience, we have concluded that in the initial treatment of thromboembolic conditions, it is hazardous and unrealistic to attempt to standardize heparin dosage or to underestimate the importance of the control of therapy by abolishing clotting time determinations or reducing their frequency to a minimum. This would seem to be especially true of acute conditions. We believe that the greatest dangers of thromboembolism are in those patients in whom therapy is most difficult to control. In this regard, our main concern is that insufficient amounts of heparin may actually aggravate the situation.

In 2 of our patients, thromboembolic relapses occurred soon (within 24 and 30 hours, respectively) after heparin therapy was stopped. Recrudescence or recurrence of thromboembolic conditions after the discontinuance of anticoagulant therapy has been reported by other authors. Inadequate or too short therapy, or both, certainly contribute to many of these failures. There is clinical and experimental evidence that, following the abrupt cessation of heparin treatment, there may be a period of rebound hypercoagulability.

It is our impression that we have had better results and a lesser incidence of complications using heparin by intermittent intravenous injection for the treatment of acute thromboembolic conditions. We attribute part of our success in treating this group of patients to the use of supplementary intravenous heparin when clotting times were unsatisfactory. We also attribute one of our failures, a fatal pulmonary embolus while on therapy, to the fact that we did not abandon subcutaneous heparin in favor of intravenous administration when it became apparent that therapy was difficult to control and the thromboembolic disorder was progressing under treatment. We thought it significant that in some patients who developed hemorrhage on subcutaneous heparin, further bleeding did not occur when therapy was continued by the intravenous route. We decided, as other workers have, that slowly absorbed heparin and dicumarol should not be used simultaneously because of the unreliability of clotting and prothrombin times under those conditions.

The successful treatment of many thromboembolic conditions requires much longer courses of anticoagulant therapy than are customarily employed. The value of subcutaneous heparin administration is that it permits the extension of definitive heparin therapy over a long period of time.

In our opinion, subcutaneous heparin should not be employed in the treatment of acute thromboembolism, after recent surgery (within 5 days) or in patients who, because of other conditions (e.g., a history of peptic ulcer), present more than the usual risk of hemorrhage. In these situations, intermittent intravenous heparin administration is the method of choice.

A summary of our present views on the treatment of patients with thromboembolism may be of interest. Proximal vein ligations are employed as initial treatment only when heparin is contraindicated. In acute and subacute conditions heparin is given intravenously by intermittent injection through a polyethylene catheter inserted into a superficial vein of the dorsum of the hand or forearm. In this manner, it is possible to treat most patients for 10 to 14 days, and many patients for a considerably longer period. This method of administration is so simple and efficacious that we prefer it to the subcutaneous route in the treatment of hospitalized patients.

Heparin is given every 4 hours. The first injection is 50 or 100 milligrams, the larger dose being used for heavier patients. Clotting times are performed 45 minutes and 3½ hours after the first injection, and subsequently, after at least 2 injections each

day. Heparin dosage is adjusted so that, regardless of the height of the peak level at 45 minutes, which may vary widely, the clotting time is near or back to the normal range just before the next injection. There is no hesitancy in giving more than 100 milligrams every 4 hours when needed, but in those cases clotting times are determined more frequently. The minimal duration of heparin therapy is 3 weeks for phlebothrombosis or thrombophlebitis without pulmonary embolism, and 4 to 6 weeks if a pulmonary embolus has occurred. In many patients, therapy is given for longer periods.

Concentrated aqueous heparin is used for all subcutaneous injections. A 12 hour schedule is employed and therapy is regulated by 6 and 11 hour postinjection clotting times as described earlier. The initial amount of subcutaneous heparin is half the total daily intravenous dose and is given in conjunction with the last intravenous injection. If the control of therapy proves difficult, intravenous administration is restarted. In the majority of patients handled in this fashion, a maintenance dose of subcutaneous heparin is readily established and remains remarkably stable. Therapy may be continued on an outpatient basis or at home. Clotting times are checked daily at first, and later several times a week if they are consistently satisfactory. A number of patients have been maintained successfully on subcutaneous heparin therapy for a month or more after discharge from the hospital. In all patients heparin therapy is discontinued gradually by giving progressively smaller, tapering, doses over a period of 4 to 5 days.

In those rare instances in which thromboses progress or pulmonary emboli occur during therapy, ligation of the inferior vena cava is performed as an emergency. Under these conditions, we believe it is unwise to attempt to improve or intensify heparin therapy, for such delay may be disastrous. When necessary, existing heparin effects are reduced by protamine sulfate. Heparin therapy is reinstituted postoperatively to preserve collateral venous channels. It has been our experience that retrograde thrombosis is not uncommon after ligation, and may involve to a greater degree the extremity which was uninvolved or least affected preoperatively.

The treatment of thromboembolism demands continued reappraisal and no regimen of therapy should be considered constant or inflexible.

SUMMARY

1. Concentrated aqueous heparin was given deep subcutaneously to a group of normal subjects and to a group of patients with thromboembolism. The effects of heparin administration were followed with clotting time determinations and blood viscosity profiles.

2. In 44 of 47 patients who received subcutaneous heparin as definitive therapy the results of treatment were satisfactory. Thrombophlebitis recurred or pulmonary emboli occurred during or following treatment in 3 patients.

3. A 12 hour interval between heparin injections was generally preferred.

4. Body weight was a helpful but not reliable guide to heparin dosage. Because of variations in heparin requirements among different patients and in the same patient from time to time, frequent clotting time determinations were necessary for the control of therapy.

5. Repeated subcutaneous injections of heparin were well tolerated and could be continued in the nonhospitalized patient.

6. With subcutaneous heparin administration, hemorrhagic complications seemed to be more frequent than with intermittent intravenous therapy.

7. The concomitant administration of subcutaneous heparin and oral dicumarol was found to be contraindicated.

8. In normal subjects and in patients with thromboembolism, the changes in blood viscosity profiles following subcutaneous heparin administration were similar to those produced by intravenous administration but were more prolonged. The degree and dura-

tion of alteration of viscosity profiles tended to, but frequently did not, parallel changes in clotting times. Pretreatment blood viscosity profiles were abnormal in about half the cases of thromboembolism.

9. We concluded that in acute thromboembolic conditions, after recent surgery, and in patients who present more than the usual risk of hemorrhage, heparin treatment should consist of intermittent intravenous injections. Subcutaneous heparin administration may be substituted after heparin requirements have been stabilized provided that the clinical course of the patient is satisfactory.

REFERENCES

1. ARTZ, C. P., and AMSPACHER, W. H. Evaluation of various methods of administration of heparin. Surgical Forum 1952; American College of Surgeons. Pp. 530–535, Vol. III. Philadelphia and London: W. B. Saunders Co., 1953.
2. ARTZ, C. P., and PULASKI, E. J. Treatment of venous thrombosis with heparin. Angiology, 1953, 4: 321.
3. ENGELBERG, H. Prolonged anticoagulant therapy with subcutaneously administered aqueous heparin. Surgery, 1954, 36: 762.
4. HURWITZ, A., YESNER, R., and COOKE, R. W. Ultrasonic measurements of the effects of heparin on blood viscosity. Laborat. Invest., 1952, 1: 436.
5. YESNER, R., HURWITZ, A., and RAUCH, A. A recalcification technique for ultrasonic measurement of blood viscosity. Laborat. Invest., 1954, 3: 312 (abstract).
6. YESNER, R., HURWITZ, A., RICH, S. R., ROTH, W., and GORDON, M. E. Preliminary observations on blood coagulation utilizing ultrasonics for continuous measurements of viscosity. Yale J. Biol., 1951, 24: 231.

INTRADUCTAL PRESSURES AND SPHINCTERIC RESISTANCE IN CANINE PANCREATIC AND BILIARY DUCTS AFTER VARIOUS STIMULI

RENÉ B. MENGUY, M.D., GEORGE A. HALLENBECK, M.D., F.A.C.S.,
JESSE L. BOLLMAN, M.D., and JOHN H. GRINDLAY, M.D., F.A.C.S., Rochester, Minnesota

AN ATTEMPT has been made to gain a better understanding of the dynamics of the pancreatic and biliary ducts and their reciprocal relationships. It was considered that such problems as the mechanism underlying the induction of hyperamylasemia in human patients by use of morphine or the close relationship between alcoholism and acute pancreatitis possibly could be clarified by study of the alterations in physiology of the pancreatic and biliary ducts produced under such conditions.

Before the work done in our laboratories by Parry and associates, information regarding the dynamics of the pancreatic and biliary ducts was limited to studies of secretory pressures. The data derived from these older studies, because of their unphysiologic nature, have been of little, if any, value in the understanding of human pancreatic disease. Therefore, we undertook to measure the pressures in the pancreatic and biliary ducts of dogs under well controlled conditions and to record the variations of these pressures, as well as the resistance of the sphincteric mechanism of the ducts, in response to various stimuli.

METHODS

Twenty-seven dogs were prepared as follows. Polyvinyl tubes, sizes 24 and 20, were introduced into the pancreatic and common bile ducts, respectively, according to the technique previously described from our laboratories (8, 13). These tubes were attached to special introducers and were placed in the ducts so that the open tip of each tube in each main duct was above the sphincter, with the remainder of the tube extending to the surface of the abdomen by way of the parenchyma of the organ in question, the peritoneal cavity, and the abdominal wall (Fig. 1). In 10 animals, No. 16 polyvinyl tubes were placed in the duodenum to record duodenal motility or to introduce various solutions directly into the duodenum. Cholecystectomy was performed in 5 animals. At least 2 weeks elapsed between the operation and the actual experiments, during which time each animal was trained to lie quietly on its side. All the studies were done with the animals unanesthetized.

Pancreatic and biliary intraductal pressures were measured by connecting the intraductal tubes to water manometers. The fluctuations of the columns of water were recorded by means of a photokymograph. This apparatus functions on the principle described by Baldes and Corbeille. The column of water in an ordinary glass tube functions as a cylindric lens, concentrating the beam of light from a punctiform source on a roll of photographic paper (Fig. 2). As the water in the tube moves up and down, the concentrated beam of light follows accordingly. The half-body thickness of the dog measured at the level of the eleventh rib with the animal lying on its side was taken as the manometric zero. The resistance of the pancreatic and

From the Sections of Surgery, Biochemistry, and Surgical Research, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

Abridgement of a portion of a thesis submitted by Dr. Menguy to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery.

biliary sphincters was measured by perfusing the ducts via the indwelling tubes with an isotonic solution of sodium chloride at body temperature under constant pressure. Control observations had shown that, under normal conditions, large amounts of solution similar to those used in the actual studies could be perfused through the ducts in this manner without any appreciable change in the rate of flow. Therefore, any significant change in the rate of flow from the control values was considered to result from variations in the resistance of the sphincteric mechanism of the perfused duct.

All the studies were undertaken with the animals under identical fasting conditions. All drugs used during the experiments were administered intravenously. The action of a given pharmacologic agent was evaluated by comparing the pressures or the sphincteric resistance measured during a preliminary control period with those recorded after the drug was given. Control observations showed that intravenous injections of isotonic solution of sodium chloride did not alter the intraductal pressures or the resistance of the sphincters.

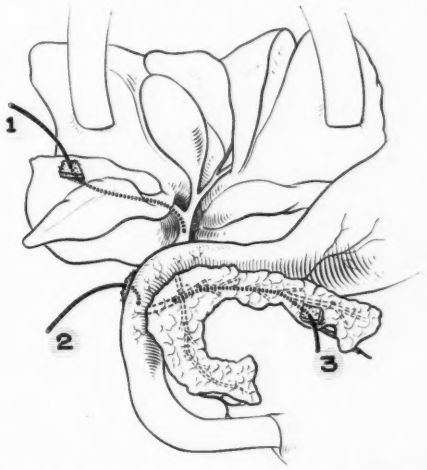


FIG. 1. Disposition of tubes in the common bile duct (*1*), duodenum (*2*), and major pancreatic duct (*3*).

RESULTS AND COMMENT

By intraductal pressure, we imply the physiologic pressure in the duct resulting from the vis a tergo of glandular secretion and the vis a fronte of the sphincteric mechanism of the duct, as modified by such factors as respiration and intra-abdominal pressure, without any extraneous factors such as perfusion of the ducts. By sphincteric resistance, we imply the resistance of the sphincteric mechanism (other factors such as the resistance of the perfusing system and of the duct itself theoretically being invariable) to perfusion of the duct.

Fasting pressures. Data on intraductal pancreatic and biliary pressures when the animals were fasting are based on control recordings taken prior to use of the various stimuli under study. Records from fasting animals were taken for 15 minutes to an hour or more, depending on the stability of the pressures at the time. The pressure in the pancreatic duct in animals with gallbladders invariably was greater than the pressure in the common bile duct. In 138 observations on 22 animals, the pancreatic intraductal pressure ranged from 35 to 293 millimeters of water, with an average of 140 millimeters. The greatest pressure (293 mm. of water) was recorded on only one occasion and probably represented spontaneous spasm of the pancreatic sphincter. The biliary intraductal pressure in 112 observations on 20 animals ranged from zero to 158 millimeters of water, with an average of 71 millimeters. In 58 observations on 5 cholecystectomized animals, the biliary pressure ranged from 23 to 256 millimeters of water, with an average of 111 millimeters. The pancreatic intraductal pressure measured simultaneously in 2 of these animals was less than the biliary intraductal pressure for prolonged periods.

The pressure in the pancreatic duct of intact dogs was characterized by its relative instability. It varied from day to day in the same dog and from one animal to another. Waves of pressure amounting to 20

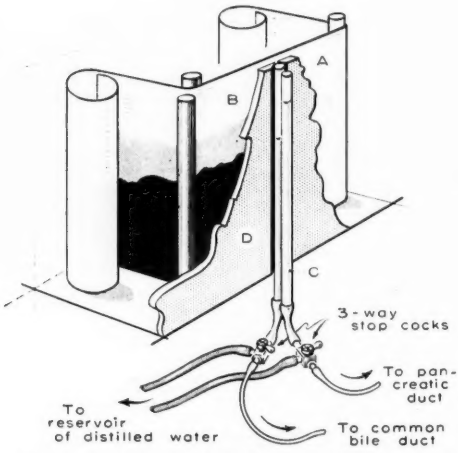


FIG. 2. Photokymograph used for recording pancreatic and biliary intraductal pressures. A beam of light from a punctiform source is concentrated through a narrow slit onto a sheet of photographic paper (*A-B*) that is driven at constant speed by a motor. The two vertical columns of water (*C*), which measure the pressures in the pancreatic and biliary ducts, vary in height with changes in intraductal pressure; these fluctuations in height are recorded on the photographic paper, enclosed in the box (*D*). Note that the image of the lower column is dark, whereas the image of the higher column, which is located anteriorly, is light.

to 30 millimeters of water and without apparent rhythmicity were not uncommon in the pancreatic duct (Fig. 3). By contrast, the biliary pressure in intact animals was stable. Waves of pressure in the bile duct were of three types: namely, type 1 waves synchronous with respiratory movements, type 2 represented by a gradual increase in pressure of from 10 to 20 millimeters, then a sharp decrease, and type 3 rhythmic waves at the rate of 1 to 2 per minute.

The biliary pressure in the cholecystectomized animals was unstable, with many type 2 waves. It was not unusual for a cholecystectomized animal to have a biliary pressure of 150 millimeters of water on one day and of 50 millimeters the next, under identical fasting conditions. There was no appreciable difference in the resistance of the biliary sphincteric mechanism between intact and cholecystectomized dogs.

Secretin and decholin. We studied the effects of an increase in secretion on the pressures in the pancreatic and biliary ducts. The stimulating action of secretin on the external secretion of the pancreas is well known. Also, bile salts are known to stimulate formation of bile by the liver in both animals and human beings. According to Bergh, the action of sodium dehydrocholate (decholin sodium) on the resistance of the biliary sphincter is slight, if any.

Intraductal pressures responded differently to increases in secretion of pancreatic juice and bile. In 4 observations on 4 animals, no change occurred in the pancreatic intraductal pressure after the intravenous administration of 10 units of secretin, despite an obvious increase in the external secretion of the pancreas as evidenced by a large flow from the cannulas when these were disconnected temporarily. In 3 observations on 3 dogs, 1 of which was cholecystectomized, the intravenous injection of 3 milliliters of decholin in a single dose was followed by an increase in biliary pressure of 40 and 63 millimeters of water in the intact dogs and of 199 millimeters in the cholecystectomized animal.

Meals. In view of the frequency with which acute pancreatitis follows ingestion of food, we studied the alterations in pancreatic pressure in response to meals. Ten observations of pancreatic intraductal pressure were made on 7 animals after a meal consisting of 450 grams of horse meat. The pressure was unaltered in 1 animal. In another dog, the meal produced an increase in the amplitude of the waves of pressure, with a slight decrease in the base line pressure. In the other animals, ingestion of the meal was followed by an increase in pancreatic pressure ranging from 6 to 84 millimeters of water. Except for 2 experiments in which a lag occurred between ingestion of the meal and the onset of the increase in pressure, the latter usually took place immediately after the animals ate.

The same protein meal had effects on the

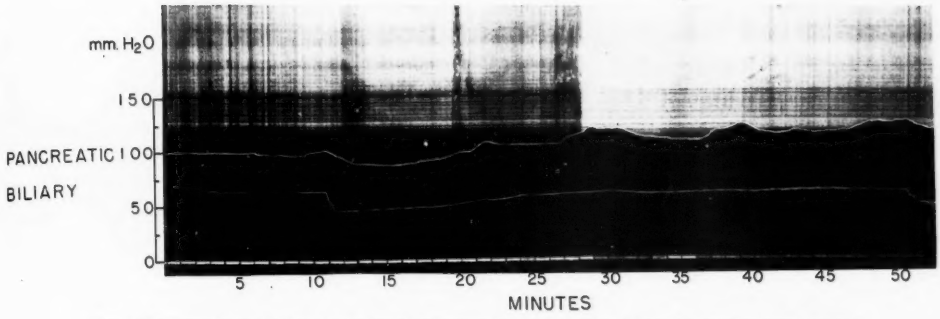


FIG. 3. Pancreatic and biliary intraductal pressures in a fasting dog. Note the greater amplitude in fluctuations of pancreatic pressure. In the biliary pressure curve, a low, type 2 wave started at 11 minutes and ended at 50 minutes.

biliary pressure that varied according to whether or not the animal had a gallbladder. In 5 observations on 4 intact dogs, a rapid increase in pressure ranging from 48 to 85 millimeters of water was noted immediately after the meal. The gradient of this increase was greater than that of the concomitant increase in pancreatic pressure, with the result that the pancreatic pressure was less than the biliary pressure for several minutes during 1 observation. An increase in the frequency of the type 3 waves of biliary pressure also was noted (Fig. 4). Eight observations were made on 5 cholecystectomized animals after ingestion of horse meat. In 2 observations on 1 animal, the biliary pressure increased by 89 and 110 millimeters of water. In the other animals, the already high biliary pressure decreased by 38 to 156 millimeters of water after the meal.

Under similar conditions, namely high fasting biliary pressure, none of the muscle relaxants that we studied produced decreases in pressure of such magnitude and duration. If the animals were fed prior to an injection of morphine, the spasmogenic action of the drug on the pancreatic and biliary sphincters was decreased greatly; in 1 instance, it was suppressed completely. This was of interest, since Walters has reported that ingestion of a meal caused partial relief in a patient who had biliary colic provoked by morphine.

Hydrochloric acid. It has been suggested that excessive acidity of the duodenal contents, by producing spasm of the pancreatic sphincter on one hand and stimulating the external secretion of the pancreas on the other, could be responsible for pancreatic intraductal stasis and pancreatic edema. On the basis of animal studies, it has been reported that application of 0.1N hydrochloric acid to the duodenum produces spasm of the biliary sphincter. Doubilet and Colp found that introduction of weak solutions of acid into the human duodenum caused transitory spasm of the sphincter of Oddi, whereas others found that acids so introduced relaxed the sphincter of Oddi.

In 8 experiments on 7 dogs, we instilled 10 milliliters of 0.1N hydrochloric acid directly into the duodenum. In 6 of these studies, the pancreatic intraductal pressure remained unaltered despite pronounced increase in the external secretion of the pancreas evidenced by large flows from the cannulas. An increase in pressure of 59 millimeters of water was noted in another experiment. In the remaining study, the response was diphasic; a transitory increase in pressure of 10 millimeters of water lasting for 2 minutes was succeeded by a prolonged decrease in pressure of 43 millimeters.

In only 1 of 6 observations on 6 intact animals was there any significant change in the biliary pressure after intraduodenal instillation of acid. This was an increase in

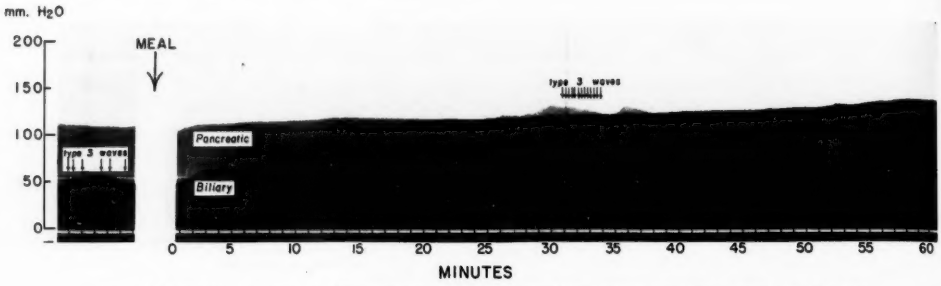


FIG. 4. Moderate increase in pancreatic and biliary intraductal pressures after a meal. This is one of several patterns observed after feeding. The increase in biliary pressure was more rapid than the concomitant increase in pancreatic pressure, with the result that biliary pressure was greater than pressure in the pancreatic duct for several minutes about 30 minutes after the meal. Note also the increase in frequency of type 3 biliary pressure waves after the meal.

pressure of 59 millimeters of water lasting for 30 minutes and apparently caused by contraction of the gallbladder. In 4 observations on 4 cholecystectomized animals, there was an increase in pressure of 72 and 159 millimeters of water in 2 instances, and a decrease of 64 and 50 millimeters in the other 2 after use of the acid. The response of the resistance of the biliary sphincter to weak acids was diphasic. In the first phase, which followed immediately after the intraduodenal instillation, there was spasm of the biliary sphincter lasting for 1 or 2 minutes; this was followed by a phase of relaxation that lasted for about 15 minutes, during which the rate of perfusion was greater than it had been during the control period.

Alcohol. A well known relationship exists between alcoholism and acute pancreatitis. The mechanism underlying this relationship has been ascribed variously to edema of the duodenum, which blocks the outflow of pancreatic juice, to a direct stimulating action of alcohol on the external secretion of the pancreas, and to the deficiencies of vitamins and proteins that accompany alcoholism. Contrary to earlier reports, good evidence exists that alcohol does not directly stimulate the external secretion of the pancreas. Other than a recent report by Nossel, who observed a slight increase of biliary pressure in 2 persons after oral intake of whiskey, no information was found in the literature regarding the action of alcohol introduced into the duodenum on the pressure in the pancreatic or biliary ducts.

A dose of 2 milliliters of 90 per cent ethyl alcohol per kilogram of body weight was introduced directly into the duodenum. This produced an increase in pancreatic pressure ranging from 30 to 100 millimeters of water in all of 6 experiments. In 2 other observations, in which the instillation was done shortly after a meal, when the increase caused by the meal had become stabilized, increases in pancreatic pressure of 124 and 111 millimeters of water, respectively, were recorded. In 4 experiments in which the same doses of 40 per cent ethyl alcohol were placed into the duodenum, increases of similar magnitude and duration occurred, namely from 40 to 110 millimeters, and lasted up to 4 hours (Fig. 5).

In 5 of 7 experiments on 4 intact animals, the biliary pressure responded to the administration of alcohol (90 per cent) by increases of from 26 to 98 millimeters of water; the pressure was not affected in the other 2 experiments. In 2 cholecystectomized animals, the instillation of alcohol (90 per cent) was followed by increases of biliary pressure of 268 and 188 millimeters of water, respectively.

Three studies were carried out in which the pancreatic and common bile ducts were

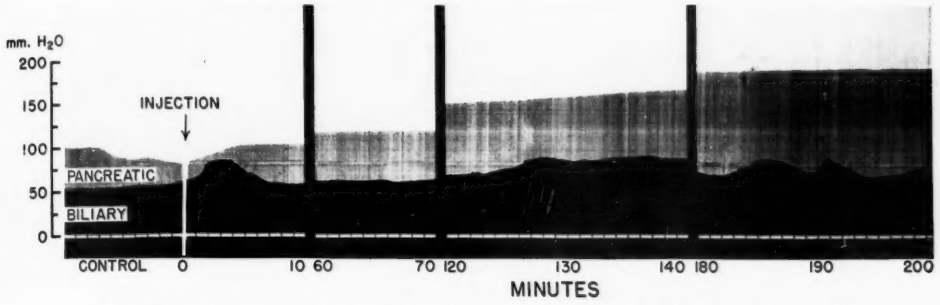


FIG. 5. Effects of intraduodenal instillation of 40 per cent ethyl alcohol (2 ml. per kilogram) on pancreatic and biliary intraductal pressures in a fasting dog. The increase in pancreatic intraductal pressure in this instance was extremely prolonged. Biliary pressure increased moderately.

perfused before and after the intraduodenal administration of alcohol. The alcohol produced a great increase in the resistance of both the pancreatic and biliary sphincteric mechanisms.

Drugs affecting the autonomic nervous system. Pilocarpine.—We could not find any studies on the action of parasympathomimetic agents on pressure in the pancreatic ducts. Some evidence indicates that the physiology of the ducts may be altered by these drugs, for an increase in plasma amylase has been observed in dogs after administration of large doses of pilocarpine or other parasympathomimetic agents. Also, an increase in plasma amylase has been noted in human beings who have chronic pancreatitis after use of small doses of neostigmine (prostigmin). An increase in biliary pressure in dogs after administration of pilocarpine has been described.

The response of the pancreatic intraductal pressure to intravenous injection of 0.2 milligram of pilocarpine per kilogram of body weight was studied in 11 experiments on 9 dogs. In 2 observations on 1 animal, a precipitous decrease in pancreatic pressure was recorded immediately after the injection, followed by a gradual increase to levels slightly greater than the control values. In the other experiments, moderate increases in pressure ranging from 12 to 64 millimeters of water were recorded. An increase in the amplitude and frequency of the waves of pressure was a feature of the response to pilocarpine (Fig. 6). In 1 ancillary experiment, pilocarpine was injected after a meal, when the increase in pressure produced by the latter had become stabilized; an increase in pancreatic pressure of 103 millimeters of water was recorded.

In contrast to what we observed of the action of other agents presumed to have a spasmogenic action on the biliary sphincteric mechanism, the changes recorded in biliary pressure after administration of pilocarpine were more pronounced in intact dogs than they were in cholecystectomized animals. In 11 observations on 9 intact dogs, the injection of pilocarpine was followed by an abrupt increase in pressure ranging from 30 to 103 millimeters of water. This initial wave was succeeded by others of less amplitude as the action of the drug waned. In 3 observations on 3 cholecystectomized animals, the injection produced an increase in pressure ranging from 61 to 65 millimeters of water, with succeeding fluctuations of less amplitude. It appeared that the action of pilocarpine on the biliary pressure was mediated more through contraction of the gallbladder than through spasm of the biliary sphincter, which would explain the lack of variation or the minimal change in biliary pressure in cholecystectomized patients after administration of parasympathomimetic agents.

In 7 perfusion experiments on 6 dogs, the

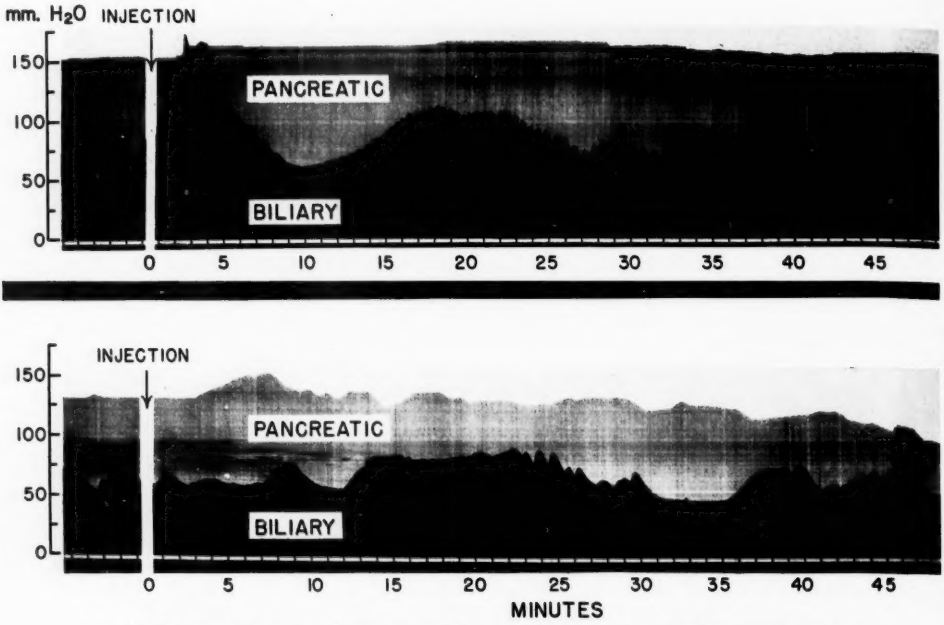


FIG. 6. Effects of pilocarpine (0.2 mgm. per kilogram) on pancreatic and biliary intraductal pressures in 2 fasting dogs. Note initial increase in biliary pressure in upper record, indicating contraction of gallbladder. This record shows definite type 3 biliary waves, which give a crenated appearance to the descending slope of the initial wave, thus indicating that they probably represent contractions of the sphincter of the bile duct. Note increase in amplitude and frequency of pancreatic pressure waves in lower record, along with slight decrease in base pressure.

aforementioned dose of pilocarpine increased the resistance of both pancreatic and biliary sphincters. This response was fluctuating in nature, with phases of increased sphincteric resistance alternating with periods during which the rate of flow was more rapid than it had been during the control period. This explained why the response of pancreatic and biliary pressures to pilocarpine was one of increased fluctuation rather than protracted increase.

Atropine.—Atropine, the prototype of parasympatholytic drugs, is known to depress the external secretion of the pancreas. However, studies of its action on the pressure in the pancreatic duct apparently have not been made. It has been reported that atropine decreases the resistance of the biliary sphincter in dogs. Other workers, on the basis of animal studies and observations on humans, claim that atropine has little, if any, effect on the resistance of the biliary sphincter or on the pressure in the common bile duct.

In 10 of 12 observations on 8 dogs, the intravenous injection of 0.15 milligram of atropine sulfate per kilogram of body weight produced a decrease in pancreatic intraductal pressure ranging from 25 to 83 millimeters of water. This decrease lasted during the entire length of the observations, namely 60 to 130 minutes after the injection (Fig. 7a). In 2 experiments on 1 animal, the pancreatic pressure was not altered by injection of atropine.

In 1 of 12 experiments on 8 intact dogs, the biliary intraductal pressure was decreased temporarily by 65 millimeters of water. In the other experiments, the biliary pressure either remained unaltered or regis-

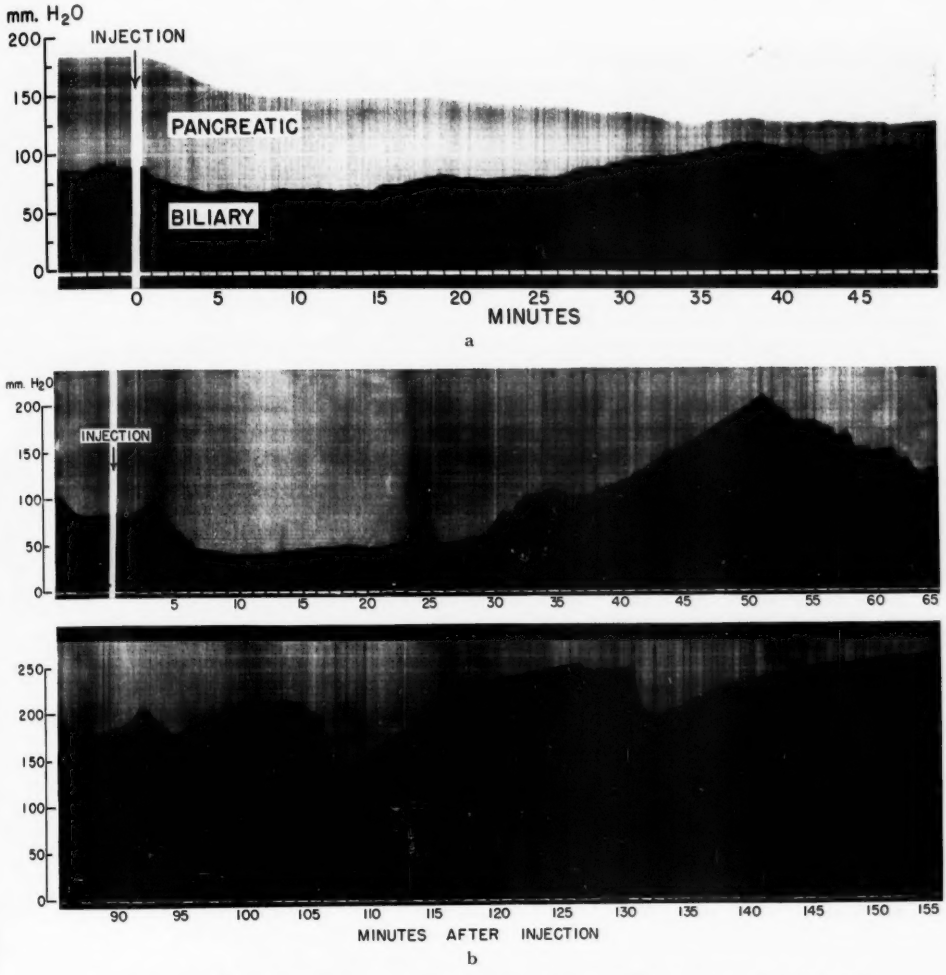


FIG. 7. Effects of atropine sulfate (0.15 mgm. per kilogram) on pancreatic and biliary intraductal pressures in dogs. a, Fasting intact dog. Note contrast between the pronounced and prolonged decrease in pancreatic intraductal pressure and the insignificant decrease in biliary pressure. The biliary pressure tends to increase after the initial decrease. b, Biliary pressure in a cholecystectomized dog (compare with "a"). The initial decrease in biliary pressure is more pronounced. After 30 minutes, biliary pressure gradually increased to definitely abnormal levels. This secondary increase is more pronounced than it is in intact dogs ("a"). The transitory decreases in pressure at 50, 105, and 130 minutes were probably due to "forcing" of the sphincteric mechanism by the great biliary pressure.

tered a slight decrease of several millimeters, followed by a rapid return to control levels. In 5 experiments on 3 cholecystectomized animals, atropine produced an immediate decrease in biliary pressure ranging from 30 to 58 millimeters of water, which was followed within 5 to 25 minutes by a gradual increase in pressure to levels appreciably greater than the control values (Fig. 7b).

TABLE I.—EFFECTS OF ANALGESICS ON PANCREATIC INTRADUCTAL PRESSURE IN FASTING DOGS

Analgesic	*Dose, mg./kg.*	*Experiments**	*Pressure, mm. of water* — *Mean increase†*	*Range of increase*	*Maximal*	*Duration of increase, minutes*
Morphine	0.2	10	104	20–205	320	55–100+
Codeine	2	6	40	24–51	242	10–110+
Methadone	0.2	3	85	48–117	277	20–120
3-Hydroxy-N-methyl-morphinan (dromoran)	0.08	2	63	49–78	233	55–75
Levorphanol tartrate (levo-dromoran)	0.05	1	60	—	205	85
Meperidine hydrochloride (demerol)	2	6	75	36–117	222	35–140

*Pressure increased in all experiments.
†Mean difference between pressure before injection and maximal pressure during 2 hours after injection. (This table is modified from Table I in Menguy, R. B., Hallenbeck, G. A., Bollman, J. L., and Grindlay, J. H. Pancreatic and biliary intraductal pressures. Surgical Forum; Clinical Congress, 1955. Pp. 359–363. Vol. VI. Chicago: American College of Surgeons, 1956).

TABLE II.—EFFECTS OF ANALGESICS ON BILIARY INTRADUCTAL PRESSURES IN CHOLECYSTECTOMIZED FASTING DOGS

Analgesic	*Dose, mg./kg.*	*Experiments**	*Pressure, mm. of water* — *Mean increase†*	*Range of increase*	*Maximal*	*Duration of increase, minutes*
Morphine	0.2	4	158	137–177	308	60–120
Codeine	2	2	192	169–215	309	100–105+
Methadone	0.2	2	172	156–188	315	60–88
3-Hydroxy-N-methyl-morphinan (dromoran)	0.08	2	201	191–222	320	40–130
Levorphanol tartrate (levo-dromoran)	0.05	2	195	183–206	310	90–140
Meperidine hydrochloride (demerol)	2	4	124	85–162	269	30–90

*Pressure increased in all experiments.
†Mean difference between pressure before injection and maximal pressure during 2 hours after injection. (This table is modified from Table III in Menguy, R. B., Hallenbeck, G. A., Bollman, J. L., and Grindlay, J. H. Pancreatic and biliary intraductal pressures. Surgical Forum; Clinical Congress, 1955. Pp. 359–363. Vol. VI. Chicago: American College of Surgeons, 1956).

In 7 perfusion experiments on 5 animals, the resistance of the pancreatic sphincter was greatly decreased by atropine. This decrease was maintained for the duration of the observations, namely 30 to 60 minutes after the injection. By contrast, the resistance of the biliary sphincter was decreased in only 2 of 7 observations on 6 dogs. In the other observations, the sphincteric resistance either remained unchanged (1 instance) or, after slight relaxation lasting for several minutes, increased to a point where, in 1 observation, the flow through the duct became completely arrested (for a perfusion pressure of 250 mm. of saline above the level of the duodenum).

Epinephrine.—It is known that stimulation of the splanchnic nerve or administration of epinephrine has a depressing action on the external secretion of the pancreas in animals. We could find no information on the response of the pancreatic pressure to injection of epinephrine. Although Doyon showed many years ago that stimulation of the splanchnic nerves produced increased tone of the biliary sphincter of dogs, the issue was confused by later reports that the administration of single doses of epinephrine to dogs either relaxed the sphincter of Oddi or had no effect. However, Johnson reported that severing the splanchnic nerves in cats enhanced emptying the gallbladder.

We administered epinephrine intravenously by means of a constant-injection pump at the rate of 1 microgram per kilogram of body weight per minute. Changes in pancreatic pressure were extremely slight and consisted of a minimal decrease in pressure during the injection. This decrease appeared to be caused by the depressant action of epinephrine on the external secretion of the pancreas. By contrast, an increase in biliary pressure was recorded during the injection, followed by a rapid return to preinjection levels after administration was discontinued. The increase in pressure was more pronounced in cholecystectomized animals than it was in intact dogs (Fig. 8).

In none of 9 perfusion experiments on 4 animals was the resistance of the pancreatic sphincter altered appreciably during the injection of epinephrine. On the other

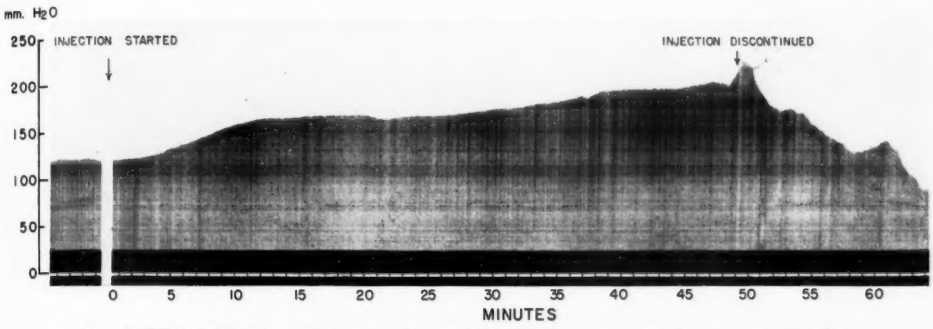


FIG. 8. Effects of continuous injection of epinephrine (1 microgram per kilogram per minute) on the biliary intraductal pressure in a cholecystectomized dog. Note gradual increase in biliary pressure during the injection, as well as absence of fluctuations in pressure curve. Immediately after injection was discontinued, biliary pressure decreased, with a concomitant increase in fluctuations of pressure curve.

hand, the resistance of the biliary sphincter invariably was increased during such injection in 12 perfusion experiments on 5 animals. Within 30 seconds to 5 minutes after the injection was discontinued, the flow during perfusion resumed its normal rate or became more rapid than it had been before injection. As evidenced by observations during which the resistance of the biliary sphincter and duodenal motility, as measured by a strain-gauge pressure transducer, were recorded simultaneously, the phase of increased sphincteric resistance during injection of epinephrine coincided with complete absence of duodenal activity, whereas a pronounced recrudescence of duodenal motility occurred when the rate of perfusion through the duct became normal after the injection of epinephrine was discontinued.

Analgesic agents. Administration of opiates increases the resistance of the biliary sphincteric mechanism in animals. These observations have been confirmed in human beings. Although studies apparently have not been made previously concerning the action of analgesic agents on the pressure in the pancreatic ducts, it is probable that such agents do affect the physiology of these ducts. It is a well confirmed observation that values for plasma amylase and lipase may be increased in human beings after injection of morphine or codeine.

We studied the action of various commonly used analgesic agents on pancreatic and biliary pressures. The drugs employed, the doses used, and the results obtained are outlined in Tables I and II. These drugs invariably produced an increase in pancreatic intraductal pressure (Fig. 9. The degree of this increase depended on the rate of pancreatic secretion at the time the injection was given; this rate could be ascertained by observing the backflow from the cannula before the experiment. One animal had an increase in pancreatic pressure of 40 millimeters of water during the first 80 minutes after injection. When the experiment was repeated several days later, the intraductal pressure in the same dog increased by 205 millimeters of water in 14 minutes; at the time of this second study, the pancreas obviously was secreting more abundantly.

In 5 of the experiments with morphine, values for plasma amylase were determined before and at intervals of 2 hours after the injection. The levels of plasma amylase did not change in 2 instances; the increases in pancreatic pressure in these 2 observations were 20 and 60 millimeters of water, respectively. In the other 3 experiments, during which the pancreatic pressure sustained increments of 205, 153, and 143 millimeters of water, respectively, transitory increases

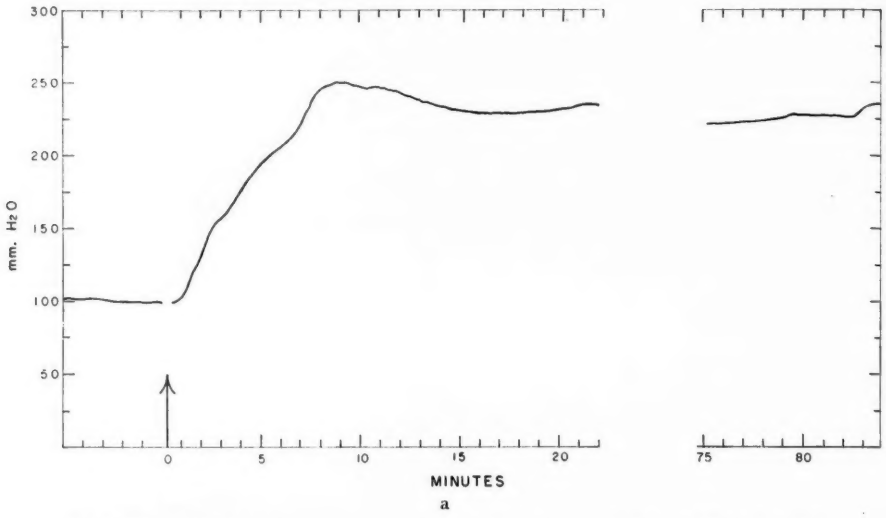


FIG. 9. Effects of analgesic agents on pancreatic and biliary pressures in dogs. a, Effect of morphine sulfate (0.2 mgm. per kilogram) on pancreatic intraductal pressure. This tracing was made from a photokymographic recording. The increase in pancreatic intraductal pressure was accompanied by a transitory increase in plasma amylase. b, Effect of morphine, illustrating the phenomenon of morphine-induced sphincteric spasm. Note amplitude of pancreatic and biliary pressure waves during control period. Immediately after injection of morphine, these waves disappeared and pancreatic pressure increased. The decreased biliary pressure is attributed to the regulating action of the gallbladder. c, Effect of demerol (2 mgm. per kilogram). Note contrast between the great increase in pancreatic pressure and the insignificant change in biliary pressure, which remained within normal limits.

in plasma amylase of 53, 111, and 204 per cent, respectively, were observed.

The biliary pressure in intact animals remained essentially unaltered after administration of these drugs. A decrease in pressure occasionally was observed. By contrast, the biliary pressure in the cholecystectomized animals invariably increased to maximal levels (Table II).

Perfusion studies showed that morphine and meperidine (demerol) hydrochloride produced an increase in the resistance of both pancreatic and biliary sphincters lasting for 1 to 3 hours. This increase in sphincteric resistance was attenuated in degree and in duration when atropine was administered with or prior to the injection of morphine. The action of morphine on the biliary sphincter was delayed; the onset of this action appeared to coincide with the onset of the second phase of the effect of morphine on duodenal motility, which is the phase of decreased motility.

Muscle relaxants. Nitrites have proved beneficial in certain cases of biliary colic. In human beings, these agents decrease the resistance of the sphincter of Oddi and the pressure in the bile duct, although this response often is extremely transitory. Similar results have been obtained with aminophylline. Papaverine hydrochloride has been reported to be ineffective in reducing the resistance of the biliary sphincter.

In 3 observations on 3 animals, 1 of which had been cholecystectomized, inhalation of a pearl of amyl nitrite decreased the pressure in the pancreatic and common bile ducts by only a few millimeters of water.

Aminophylline administered intravenously in doses of 10 milligrams per kilogram

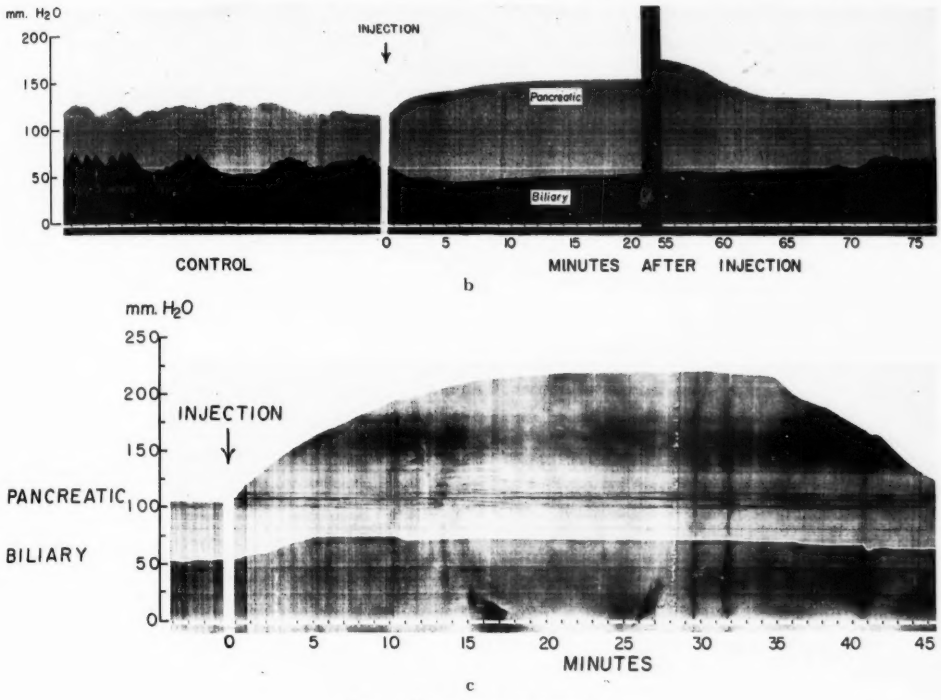


FIG. 9. (*Legend on opposite page.*)

caused a decrease in pancreatic pressure ranging from 22 to 72 millimeters of water in all of 3 experiments. Whereas biliary pressure in intact animals remained unaltered after the injection of aminophylline, the already high biliary pressure decreased by 72 and 93 millimeters of water, respectively, in 2 experiments on cholecystectomized animals.

In 8 studies on 5 dogs, 1 milligram of papaverine hydrochloride per kilogram was injected intravenously. In 2 instances, the pancreatic pressure decreased by 25 and 60 millimeters of water, respectively. In the other observations, the pancreatic pressure remained unchanged. In none of the 8 experiments on intact dogs did the biliary pressure change. In 3 experiments on 3 cholecystectomized dogs, the biliary pressure decreased by 138 millimeters in 1 instance and was unaffected in the other 2.

GENERAL COMMENT

It is commonly postulated but never has been proved that acute pancreatitis in man might be initiated by reflux of bile into the pancreatic ducts via a "common channel" after obstruction of the ampulla of Vater. If pancreatic and biliary intraductal pressures in man behave like those in the dog, reflux of bile into the pancreatic ducts would not occur because pressures are almost always greater in the pancreatic duct than in the bile duct. However, biliary pressures in cholecystectomized animals sometimes exceeded pancreatic pressures. If this is true in man, one might consider that the pressure relationships could permit passage of bile from the biliary to the pancreatic ductal systems in patients who had nonfunctioning gallbladders or after cholecystectomy. One could oppose this last statement with the argument that the maximal secre-

tory pressure of the pancreas is greater than that of the liver. Jordan and Hallenbeck found that, if the pancreatic duct was obstructed, the pancreatic secretory pressure rapidly increased to as much as 440 millimeters of water, a value greater than that generally accepted as the maximal secretory pressure of the liver. However, these initial peaks were not maintained and were followed by a gradual decrease in secretory pressure to values that were 100 to 200 millimeters less than the maximum. Pancreatic secretory pressures as low as 180 millimeters of water occurred periodically in 3 of 4 animals in their study. Whether reflux of bile into the pancreatic ducts actually takes place in man or is of any consequence is another problem.

The variation in secretory pressure of the obstructed pancreas may explain why identical doses of morphine in our experiments produced increases in pancreatic intraductal pressure of different magnitude from day to day. This observation contrasted with the biliary pressure, which invariably increased to maximal levels after injection of morphine or similar drugs.

A mere increase in the rate of external secretion of the pancreas did not alter the pressure in the pancreatic duct, whereas a similar stimulus caused an increase in biliary pressure. Thus, it appears that, in the dog at least, the biliary sphincteric mechanism represents a more efficient obstacle to the flow of intraductal fluid into the duodenum than does the pancreatic sphincter, perhaps because of the more oblique disposition of the intramural segment of the common bile duct.

The observation that the resistance of the biliary sphincter was increased by epinephrine appears somewhat paradoxic, for epinephrine is known to relax the smooth muscle of the intestine. However, the milking action of duodenal peristalsis, as pointed out by Burget, is a factor in the drainage of bile into the duodenum, and the suppression of this milking action by epinephrine partially could explain this increase in biliary sphincteric resistance. An additional explanation for this apparent paradox may reside in the fact, demonstrated by King and Robinson in dogs, that the muscularis mucosae responds to epinephrine by contraction, whereas the muscularis propria responds by relaxation. This occurred in vivo and in vitro. Contraction of the muscularis mucosae surrounding the papilla of the common bile duct could be a factor in obstruction. Our observations with epinephrine may explain the increase in biliary pressure that Doubilet recorded in human beings during emotional upsets.

Atropine was far more effective in reducing pancreatic intraductal pressure than were the muscle relaxants, namely amyl nitrite, aminophylline, and papaverine hydrochloride. The finding that atropine did not cause any appreciable decrease in biliary pressure brings us back to the observation that inhibition of duodenal motility apparently impeded, rather than enhanced, the flow of bile. For instance, not only was ingestion of a meal much more effective than use of atropine in decreasing biliary pressure in cholecystectomized dogs in face of spontaneous spasm of the biliary sphincter but a meal also was slightly more effective in attenuating the spasmogenic effects of morphine.

The increase in pancreatic pressure after use of small doses of pilocarpine could account for the increase in plasma amylase that has been observed in dogs after administration of large doses of pilocarpine. In our studies, during which the animals were unanesthetized, the doses had to be kept small, for an uncomfortable animal would have invalidated any pressure recordings.

Instillation of weak solutions of acids into the duodenum produced variable effects on the biliary pressure. Increases and decreases in pressure occurred with equal frequency in the cholecystectomized animals. Hydrochloric acid apparently did not have any spasmogenic effects on the pancreatic sphincter, especially since its intraduodenal instillation was followed by a pronounced

increase in pancreatic secretion, during which any appreciable increase in sphincteric resistance would have been obvious.

In some of our experiments with morphine, an increase in plasma amylase coincided with a great increase in pancreatic intraductal pressure. It is probable that the increase in plasma amylase or lipase in human beings after injection of morphine is on a similar basis. Reflux of bile into the pancreatic duct, which has been suggested as a possible mechanism for morphine-induced hyperamylasemia, was precluded in our studies, since there is no communication between the pancreatic and biliary ducts in the dog. The absence of any concomitant increase in biliary pressure is explained by the regulating action of the gallbladder on biliary pressure and by the fact that morphine has no action on the musculature of the gallbladder. We suspect that the spasmogenic effect of the analgesic drugs, including demerol, is entirely mediated by the sphincteric action of the duodenal muscle surrounding the intramural segment of these ducts. As shown by Vaughn Williams and Streeten, the fundamental effect of these agents on the smooth muscle of the intestine is prolonged contracture. Although Eichhorn and Boyden recently described an anatomically independent sphincter of Oddi in the dog, they considered that the function of the biliary sphincteric mechanism was largely dependent on the activity of the surrounding duodenal muscle. The few histologic sections that we made did not indicate the presence of a pancreatic sphincter anatomically independent of the surrounding duodenal fibers. Thus, it can be inferred that in human beings the outlet of the duct of Santorini, as well as that of the duct of Wirsung, would be involved in the action of morphine and similar drugs.

The increase in pancreatic intraductal pressure observed after the introduction of 40 per cent and 90 per cent alcohol into the duodenum could explain the frequent occurrence of acute pancreatitis after a large intake of alcohol.

SUMMARY

By means of a method of measuring pancreatic and biliary intraductal pressures that leaves the sphincteric mechanisms of the ducts intact, studies have been made in dogs of the responses of these pressures to various stimuli.

The pancreatic intraductal pressure was always greater than the pressure in the common bile duct. After cholecystectomy had been performed, the biliary pressure was greater than it was in intact animals and sometimes exceeded the pressure in the pancreatic duct.

Observations were made on the effects produced on the physiologic function of these ducts by meals and by the intraduodenal instillation of acid and alcoholic solutions. A study also was made of the changes produced by the administration of various analgesic and autonomic drugs and muscle relaxants.

REFERENCES

1. Baldes, E. J., and Corbeille, C. Photographic method of recording plethysmograms. Proc. Soc. Exp. Biol., N. Y., 1929, 26: 711–715.
2. Bergh, G. S. Sphincter mechanism of common bile duct in human subjects; a study of its reaction to certain types of stimulation. Surgery, 1942, 11: 299–330.
3. Burget, G. E. The regulation of the flow of bile; II, effect of eliminating the sphincter of Oddi; III, the role of the gall bladder. Am. J. Physiol., 1925, 74: 583–589; 1926, 79: 130–134; 1927, 81: 422–430.
4. Doubilet, Henry. Section of the sphincter of Oddi; principles and technique. Surg. Clin. N. America, 1956, August, pp. 865–882.
5. Doubilet, Henry, and Colp, Ralph. Resistance of the sphincter of Oddi in the human. Surg. Gyn. Obst., 1937, 64: 622–633.
6. Doyon, M. De l'action exercée par le système nerveux sur l'appareil excréteur de la bile. Arch. de physiol. norm. et path., Par., 1894, 5.s.6: 19–31.
7. Eichhorn, E. P., Jr., and Boyden, E. A. The choledochoduodenal junction in the dog; a restudy of Oddi's sphincter. Am. J. Anat., 1955, 97: 431–451.
8. Grindlay, J. H., Eberle, Johannes, and Walters, Waltman. A technique for external drainage of the biliary tract which leaves the ducts intact; an experimental study. Arch. Surg., 1953, 67: 289–296.
9. Johnson, F. E. Effect upon the biliary tract of sectioning the splanchnic nerves. Proc. Soc. Exp. Biol., N. Y., 1941, 47: 399–400.
10. Jordan, G. L., Jr., and Hallenbeck, G. A. A study of the effect of increased secretory pressure on canine pancreatic secretion. Am. J. Physiol., 1952, 170: 211–216.

11. KING, C. E., and ROBINSON, M. H. The nervous mechanisms of the muscularis mucosae. Am. J. Physiol., 1945, 143: 325–335.
12. NOSSEL, H. L. The effect of morphine on the serum and urinary amylase and the sphincter of Oddi; with some preliminary observations on the effects of alcohol on the serum amylase and the sphincter of Oddi. Gastroenterology, 1955, 29: 409–416.
13. PARRY, E. W., HALLENBECK, G. A., and GRINDLAY, J. H. Pressures in the pancreatic and common ducts; values during fasting, after various meals and after sphincterotomy; an experimental study. Arch. Surg., 1955, 70: 757–765.
14. VAUGHN WILLIAMS, E. M., and STREETEN, D. H. P. The action of morphine, pathidine, and amidone upon the intestinal motility of conscious dogs. Brit. J. Pharm., 1950, 5: 584–603.
15. WALTERS, WALTMAN. The pathological physiology of stone in the common bile duct. Surg. Gyn. Obst., 1936, 63: 417–424.

THE SURGICAL DIAGNOSIS AND MANAGEMENT OF DYSFUNCTIONAL UTERINE BLEEDING

EQUINN W. MUNNELL, M.D., F.A.C.S., and FERDINAND H. FLICK, M.D., New York, New York

BLEEDING FROM THE UTERUS due to unknown, benign causes has been called by various terms, among them, dysfunctional bleeding. We have applied this term to a study of 464 hospitalized patients admitted to the Sloane Hospital for Women (Columbia-Presbyterian Medical Center) during the years 1931 to 1945, with a surgical diagnosis of menorrhagia, metrorrhagia, or both and in whom pathologic investigation showed the bleeding not to be due to neoplasms, inflammations, or pregnancy. The causes of vaginal bleeding may be summarized as follows:

Organic: (1) in early pregnancy—abortion, ectopic, mole, unknown; (2) inflammatory—salpingo-oophoritis, endometritis, cervicitis, vaginitis (senile); (3) neoplasms—benign: fibroids and polyps; malignant: carcinomas of cervix, endometrium, and ovary.

Functional: (1) hyperplasia—cystic glandular and adenomatous; (2) unknown. This study is concerned with the functional causes of abnormal bleeding when diagnostic curettage has excluded neoplasms and pregnancy as possible causes.

When treating the patient whose complaint is menorrhagia or metrorrhagia or both, the gynecologist must first determine whether or not the type of bleeding falls within normal limits and is, therefore, only a variation of the normal. Bleeding may occur as often as every 21 days and still represent normal menstruation. Bleeding between periods, or metrorrhagia, cannot be considered normal. Duration and amount of flow vary considerably with different women and here the gynecologist must fall back upon such criteria as whether or not there has been a departure from the usual pattern of the particular patient. Having decided his patient's bleeding is abnormal but being unable to make a positive diagnosis after examination, he must then determine whether he may safely observe his patient (perhaps making usually unsatisfactory endocrine attempts to treat here in the meantime) or whether he should perform a dilatation and curettage. He will be influenced in making this decision by the patient's age and relation to the menopause as well as by the duration of her symptoms. His concern is first to rule out malignant tumor and secondly to arrest the bleeding. Let us assume he performs the curettage and determines that his patient has no tumor, benign or malignant, but is suffering from functional bleeding. What was its cause? Will the bleeding recur? What future problems may the patient encounter? These are some of the questions pertinent to this study as well as an attempt to answer the often asked question, "How many dilatations and curettages before hysterectomy is indicated?"

From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, and the Department of Obstetrics and Gynecology, Presbyterian Hospital (Sloane Hospital for Women), New York.

ETIOLOGIC BACKGROUND

Theories. The prevalent opinion is that the underlying cause of dysfunctional uterine bleeding is a hormonal disturbance. The chief evidence supporting this theory lies in the early experiments on ovariectomized animals and in the known effects of ovarian hormones on the uteri of ovariectomized or postmenopausal women. These theories explain a possible immediate cause, that an ovarian derangement exists, but fail to explain why the ovarian hormone balance has changed.

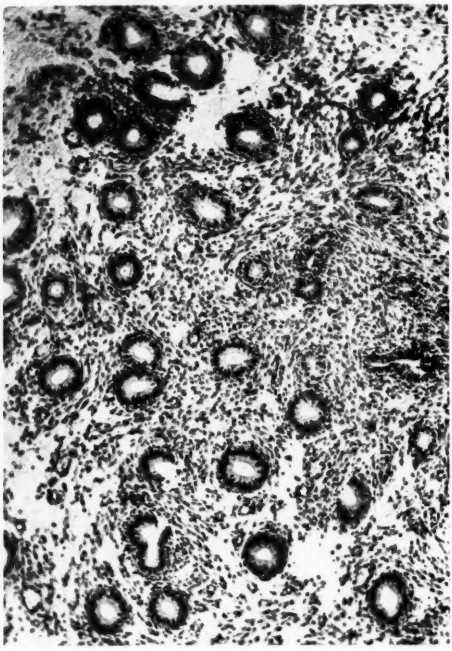


FIG. 1. Photomicrograph showing active proliferative endometrium.

Another theory relates dysfunctional bleeding to the effects of autonomic drugs on the uterine vasculature. Hechter, Lev, and Soskin found that estrogen liberated acetylcholine could be inhibited by atropine and that uterine hyperemia and vascular distention were markedly lessened in atropinized mice given estrogen. Soskin, Wachtel, and Hechter demonstrated that prostigmine clinically overcame a poor uterine vascular response by inactivating choline esterase and potentiating the naturally present acetylcholine. This reaction can be employed as a therapeutic test for pregnancy.

TABLE I.—MICROSCOPIC DIAGNOSIS OF 464 CASES OF DYSFUNCTIONAL UTERINE BLEEDING

	No. cases	*Per cent*
Proliferative endometrium	177	38
Secretory endometrium	113	24
Cystic glandular hyperplasia	60	13
Premenopausal 50		
Postmenopausal 10		
Adenomatous hyperplasia	15	3
Premenopausal 11		
Postmenopausal 4		
Postmenopausal, nonhyperplasia	60	13
Insufficient tissue	23	5
Atrophy of endometrium	8	2
Irregular shedding	8	2
Total	464	100

The connection between the uterine vasculature and the autonomic nervous system may explain amenorrhea in physical and emotional stress states.

Pathologic review. Examination of the pathologic material in this series of 464 cases resulted in the microscopic diagnoses summarized in Table I. In almost two-thirds of all cases normal proliferative or normal secretory endometrium was obtained. Third in frequency, but much less common, was hyperplasia usually of the cystic glandular type.

In 38 per cent of the curettings proliferative endometrium was obtained. Figure 1 shows active proliferative endometrium with round, straight, endometrial glands lined by polystratified columnar epithelium. No vacuoles, evidence of secretory activity, are present. Active growth is evident from the presence of mitotic figures.

About half of the patients with proliferative endometrium were found to have had curettage more than 2 weeks after the last menstrual period had occurred. Some evidence of secretory activity should have been evident in these endometria but was not. The assumption, therefore, is that ovulation was not occurring in these patients and that the absence of ovulation may have been responsible for abnormal bleeding. These cases of "anovulatory bleeding" are summarized as follows: in 69 cases a dilatation and curettage was performed less than 2 weeks after the last menstrual cycle, in 72 cases more than 2 weeks after, and in 36 cases these data were unknown.

We were interested in thickening of the endometrial arterioles on the assumption that this thickening gives them a certain inelasticity so that they are unable to regulate the menstrual bleeding properly. Figure 2 is an example of this type of endometrium with thickened arterioles. Twenty such cases were found in this series and it seemed a

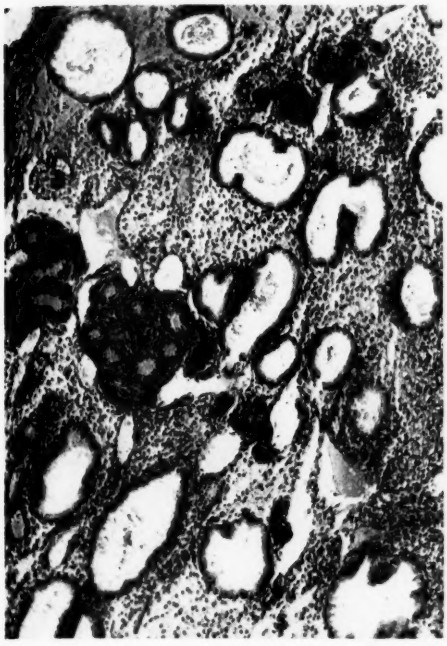


FIG. 2. Photomicrograph showing the thickened arterioles.

FIG. 3. Photomicrograph showing secretory endometrium.

promising lead until it was shown also to be present in endometrium from many patients without a history of abnormal bleeding. Therefore, we believe it cannot be considered a causative factor in dysfunctional uterine bleeding.

Twenty-four per cent of the 464 cases of microscopic material showed secretory endometrium (Fig. 3). Secretory endometrium is the endometrial response to the corpus luteum hormone characterized histologically by varying degrees of glandular tortuosity and a single layer of epithelium containing vacuoles which are basal when they first appear shortly after ovulation and are irregularly distributed throughout the cell later in the cycle. Why patients with normal secretory endometrium have abnormal bleeding is hard to explain.

Aptly described as the "swiss cheese pattern," cystic glandular hyperplasia is often grossly hyperplastic and microscopically characterized by the findings of large, dilated endometrial glands with a dense stroma. Normal glands are also seen. Columnar epithelium of nonsecretory type is seen unless the cystic gland has flattened out the epithelium. Schröder (5) calls attention to thromboses of the vessels and to areas of infarction as being the causes of bleeding in these cases.

Cystic glandular hyperplasia was the third most common type of endometrium found. The 60 such cases made up 13 per cent of the total. It is quite possible that this figure should be higher for we know the disease is characterized by remissions and that patients, who at one endometrial sampling show cystic glandular hyperplasia, may at another time show proliferative endometrium. Figure 4 shows cystic glandular hyperplasia as it appears under microscopic examination.

Adenomatous hyperplasia has been shown

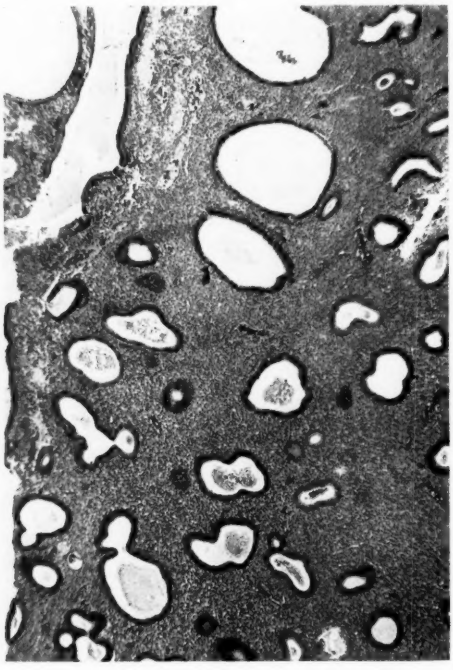


FIG. 4. Photomicrograph showing cystic glandular hyperplasia of the endometrium.

by Taylor, Gusberg and associates, Te Linde and associates, Speert, and others to be an occasional precancerous lesion, and therefore assumes considerable importance. It was found in 15 of the 464 cases, an incidence of 3 per cent. Figure 5 shows the glandular tufting and anaplasia seen in this disease. The dense stroma, increased number of endometrial glands, and the increase in the polystratified layers of endometrial cells are all characteristic of adenomatous hyperplasia. Adenomatous hyperplasia often has coexisting cystic glandular hyperplasia since estrogenic stimulation may be responsible for the occurrence of both histologic pictures.

TABLE II.—AGE IN RELATION TO PATHOLOGIC DIAGNOSIS

Pathologic diagnoses	*Average age, yrs.*	*Youngest, yrs.*	*Oldest, yrs.*
Proliferative endometrium	36	12	52
Secretory endometrium	35	17	52
Cystic glandular hyperplasia ..	36	15	62
Adenomatous hyperplasia	41	32	59
Atrophic endometrium.....	58		
Irregular shedding.....	45		
Insufficient tissue.....	59		

Irregular shedding was the diagnosis in 8 cases, an incidence of 2 per cent. This infrequently encountered finding is thought to be due to subthreshold amounts of progesterone, insufficient to prolong the cycle but sufficient to interfere with normal shrinkage, shedding, involution, and healing. There is a marked alteration in blood vessel appearance in this pathologic picture, there being an excessive number of venous sinusoids and arterioles.

There were 60 cases of benign postmenopausal bleeding. These included atrophic endometrium or endometrium insufficient for diagnosis. There were, however, 9 patients with normal proliferative endometria only 1 of whom had received estrogens; the dates of the last normal menstrual periods were 2, 1, 1, 1, 3, 4, 2, and ½ years prior to the curettage for postmenopausal bleeding. At least 4 of these might be said to have been having normal menstruation instead of postmenopausal bleeding.

The clinician is occasionally called upon to decide whether a patient in her menopausal years is having postmenopausal bleeding or a considerably delayed menstruation. His decision would best be made by taking into account the amount and duration of bleeding in a woman who has not menstruated in some months. Any doubt should be dispelled by a diagnostic curettage.

Atrophic endometrium looks like inactive proliferative endometrium with no mitoses and has a fibrous stroma with a smaller number of glands than that encountered in active proliferative endometrium.

The slides of the entire group were carefully reviewed in an effort to demonstrate some fairly uniform finding in normal endometria. As already evident, none was found. Lack of ovulation accounted for bleeding in some. The thickened blood vessels were only occasionally encountered. In the majority of cases with proliferative and

secretory endometrium, the cause of bleeding was not apparent histologically.

CLINICAL FACTORS

Table II shows the average age of patients according to the different microscopic diagnoses. The older age groups were more apt to show atrophic endometrium or insufficient tissue as one would expect. Adenomatous hyperplasia was seen in a somewhat older age group than was cystic glandular hyperplasia.

There was absolutely no correlation between pattern of bleeding and microscopic diagnosis. All types of bleeding patterns were seen with different types of microscopic pictures.

Very few patients in this group were found to have a hemoglobin below 70 per cent (Sahli). Only 31, or 7 per cent, of the 464 patients were found to be anemic. These were scattered throughout the different types of pathologic findings with no predilection for any particular microscopic picture. These findings are summarized in Table III.

In the past, frequently considered culpable for many a functional gynecologic complaint but slowly relinquishing this position is hypothyroidism. The considerable number of patients in whom investigation of the thyroid was carried out is evidence of the widespread belief in the fact that thyroid dysfunction is frequently responsible for menstrual abnormalities. However, insofar as excessive or dysfunctional uterine bleeding is concerned, thyroid function, as measured by the basal metabolic rate, is generally normal. A summary of these findings in the present series indicated that the basal metabolic rate was less than −10 per cent in only 6 cases or 1.5 per cent and over +10 per cent in only 19 cases or 4.8 per cent. Thyroid function was normal in 366 cases and unknown in 73 cases of the group. In spite of the lack of correlation between menstrual abnormalities and abnormal basal metabolic rates, thyroid extract has long been advised on an empiric basis. We see no indication for its empiric use in dysfunctional bleeding.

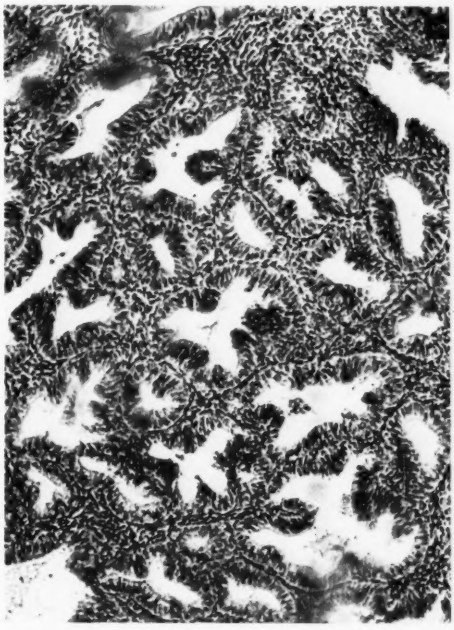


FIG. 5. Photomicrograph showing adenomatous hyperplasia of the endometrium.

Sixty-six per cent of these 464 patients were known to have had one or more successful previous pregnancies. Of the patients with hyperplasia, 64 per cent prior to developing hyperplasia had had one or more successful term pregnancies and were therefore not different from the nonhyperplasias. However, there was a great difference between the hyperplasia group and others when it came to the pregnancies *after* curet-

TABLE III.—ANEMIA (HEMOGLOBIN UNDER 70 PER CENT SAHLI)

Pathologic diagnoses	*Total No. blood counts*	*No. patients with anemia*
Proliferative endometrium	177	13
Secretory endometrium	113	2
Cystic glandular hyperplasia	60	9
Adenomatous hyperplasia	15	2
Atrophic endometrium	8	1
Irregular shedding	8	2
Insufficient quantity	23	2
Total	404	31 (7 per cent)

TABLE IV.—SURGICAL THERAPY INITIALLY EMPLOYED IN 464 CASES

Method	*No. cases*	*Per cent*
Dilatation and curettage	382	82
Dilatation and curettage plus radium or x-radiation	61	13
Hysterectomy	21	5
Total	464	

tage. Only 1 patient with cystic glandular hyperplasia became pregnant subsequently and she was one with at the most, very mild hyperplasia. There were numerous subsequent pregnancies in the groups with proliferative or secretory endometrium.

SURGICAL MANAGEMENT AND ITS EFFECTIVENESS

Methods. In Table IV the primary methods of surgical treatment are summarized. Usually this was curettage, performed in 382 cases or 82 per cent of the total. Dilatation and curettage and radium, or much less commonly, x-ray castration, constituted the initial treatment in 13 per cent, and 5 per cent of the patients were initially treated by hysterectomy.

Results. The effectiveness of curettage and radiation castration is summarized in Table V. Dilatation with curettage is generally considered primarily a diagnostic procedure. That it is a highly effective therapeutic measure in cases of dysfunctional bleeding is evident from results shown in Table V.

In those instances in which dysfunctional bleeding was on a nonhyperplasic basis, curettage produced immediate cure of the bleeding in 87 per cent of the cases. This cure was permanent in two-thirds of the cases. Sixty-five (or 21 per cent) of the patients were temporarily cured of the abnormal bleeding but had recurrence of bleeding in forthcoming years. We have included as recurrent cases any patient returning with bleeding due to any cause other than pregnancy. Thus, patients returning 6 or 7 years later with fibroids, polyps, hyperplasia, or cancer are included in this group of recurrences: Of the 65 recurrences only 34 were caused by dysfunctional bleeding.

When curettage failed to cure or there was subsequent recurrence of bleeding, no subsequent treatment was needed in about one-fourth of the cases, spontaneous cessation of abnormal bleeding taking place without treatment. Of the recurrences due to nonhyperplastic dysfunctional bleeding treated by a second curettage 60 per cent were cured and 40 per cent later recurred. Thus, a very high percentage of patients with recurrent dysfunctional bleeding *not* due to hyperplasia were either spontaneously cured or cured permanently by a second curettage, thus justifying the conservative method of approach in nonhyperplastic bleeding.

When abnormal bleeding was due to hyperplasia, immediate relief from bleeding was obtained in 72 per cent of the cases. However, the chance of recurrence or of immediate failure is much greater with hyperplasia, being 69 per cent in this group as shown in Table V. Twenty per cent of the patients with hyperplasia had had one or more curettages elsewhere before coming to us. Cystic glandular hyperplasia therefore is a persistent, recurrent disease.

Eighty-four patients in this group received curettage and radium or, in a very few cases, deep x-ray therapy. The doses administered were generally in the amount of 2,000 to 2,250 milligram hours of radium. Of these 84 patients, 55 received dilatation and curettage and radium as primary treatment, while the remaining 29 had a previous curettage either in this hospital or elsewhere. It will be seen that the chance of immediate cure is 100 per cent in both the nonhyperplasias as well as in the hyperplasias. However, the possibility of subsequent recurrence of bleeding is significant as seen in Table V with 13 of 84 patients or 15 per cent subsequently having recurrent bleeding. Of these 13 patients with subsequent bleeding the administration of estrogens accounted for it in at least 2 cases and an adenocarcinoma of the endometrium in 1 case. Of these 13 recurrences 6 patients required repeat dilatation and curettage and

2 required hysterectomy. Six of the 13 failures had had radium for benign postmenopausal bleeding.

The 1 death in the entire series occurred on the fourth postoperative day in a patient whose initial treatment for dysfunctional bleeding was hysterectomy; this was an operative death. Another patient who had subtotal hysterectomy initially performed for dysfunctional bleeding required diagnostic curettage of the cervical stump years later because of bleeding. In all, 56 hysterectomies were done in this group. In 21 cases it was the initial therapy employed in this hospital; in the remaining cases it was done for recurrent bleeding or for the development of fibroids or carcinoma.

TABLE V.—EFFECTIVENESS OF SURGICAL THERAPY

	*Dilatation and curettage**		*Dilatation and curettage plus radium*	
	No.	*Per cent*	*No.*	*Per cent*
Nonhyperplasia				
Permanent cure	208	66	52	83
Immediate cure but recurred	65	21	11	17
Failed	41	13	0	0
Hyperplasia				
Permanent cure	17	31	19	90
Temporary cure but recurred	22	41	2	10
Failed	15	28	0	

*Includes 28 patients with 2 dilatations and currettages.

HYPERPLASIA

The hyperplasias made up 16 per cent of the total number of cases of dysfunctional bleeding. Most of these were patients with cystic glandular hyperplasia (60) and a smaller number (15) had adenomatous hyperplasia.

Previous fertility was normal, 64 per cent of these patients having had one or more successful term pregnancies. Subsequent fertility, however, was so low that only 1 out of the entire 75 patients became pregnant after the disease was diagnosed, and this 1 patient had a pathologic diagnosis of very mild cystic glandular hyperplasia. This figure is to be compared with about 10 per cent subsequent pregnancies in the nonhyperplasia group. A slightly higher average age in the hyperplasias, 39.5 years, is a contributing factor.

Ten per cent of patients with cystic glandular hyperplasia had oligomenorrhea as well as menorrhagia or metrorrhagia.

A few patients with endometrial samplings before or after diagnosis was made had proliferative or secretory endometrium thus illustrating the fact that cystic glandular hyperplasia and adenomatous hyperplasia may disappear and recur.

Twenty per cent of patients with hyperplasia had had dilatation and curettage one or more times in other hospitals before coming to Sloane for curettage. Of the patients with hyperplasia curetted in this series 78 per cent subsequently had recurrent bleeding of a dysfunctional nature except for 1 case of fibroids, 1 of adenomyosis interna, and 2 cases of endometrial adenocarcinoma. Thus, hyperplasia of the endometrium is a persistently recurring disease characterized by marked diminution in fertility potential.

The 2 cases of adenocarcinoma developing sometime after dilatation and curettage for dysfunctional bleeding both followed adenomatous hyperplasia, not cystic glandular hyperplasia. It is an accepted fact now that adenomatous hyperplasia is occasionally a precancerous lesion. How often it goes on to cancer is a statistical figure not reliably answered by the small number of cases in this series but it seems to be between 10 and 15 per cent. The clinician should be well aware of the fact that pathologic evaluation of adenomatous hyperplasia is difficult.

No case of cystic glandular hyperplasia in this series of 60 went on to adenocarcinoma. Cystic glandular hyperplasia has not been considered a precancerous lesion although adenomatous hyperplasia has been and the two are often present together. Cases of coexisting adenocarcinoma, adenomatous hyperplasia, and cystic glandular hyperplasia are not uncommon. But a clear course of progression from cystic glandular hyperplasia to adenomatous hyperplasia remains to be proved. Nevertheless, until this relationship is better understood, it would seem

TABLE VI.—SUBSEQUENT ORGANIC DISEASE, BASED ON 414 CASES WITH AN AVERAGE FOLLOW-UP OF 3 YEARS AND 4 MONTHS

	Hyperplasias	*All others*
Fibroids	1	20
Polyps	0	2
Cystic glandular hyperplasia	0	3
Adenomyosis	1	0
Carcinoma		
Cervix	0	2
Endometrium	2	2
Ovary	0	2

safer to resort to hysterectomy rather than radiation castration for final treatment of recurrent cystic glandular hyperplasia.

SUBSEQUENT DEVELOPMENT OF OTHER DISEASES

From Table VI it is apparent that fibroids subsequently developed in about 6 per cent of these patients during an average follow-up period of 4 years. Eight cases of genital carcinoma developed, 2 each of cervix and ovary, and 4 of endometrium. The 2 endometrial cancers in the hyperplasias both followed cases of adenomatous hyperplasia. This observation has already been discussed.

RECOMMENDED MANAGEMENT OF UTERINE BLEEDING OF UNKNOWN CAUSE

Curettage. Curettage offers such good results as a therapeutic measure in treating dysfunctional bleeding that radiation castration should probably be used for this purpose only rarely as the first treatment regardless of the age group being treated. Hysterectomy should never be chosen as initial treatment.

Curettage has a dual function. First, it establishes a pathologic diagnosis. Second, it offers a good chance of cure if the bleeding is functional in origin.

Abnormal uterine bleeding on a dysfunctional basis occurs with great frequency and curettage cannot be done for every patient who has an isolated episode of menorrhagia, metrorrhagia, or menometrorrhagia and who has an apparently normal pelvis. The patient's age, whether she is premenopausal or postmenopausal, the duration of symptoms, and the persistence of symptoms must all be considered in deciding upon the need for curettage. The postmenopausal patient should be curetted promptly upon the occurrence of bleeding in view of the high incidence of cancer as the cause of bleeding in the postmenopausal patient. In younger women one might temporize depending upon the duration of symptoms. Women in their forties with one episode of abnormal bleeding might have Papanicolaou smears and endometrial biopsy performed with the realization that these procedures are not as good as curettage as diagnostic measures; with recurrence or persistence of bleeding in this age group, curettage is indicated even if smears and biopsy are negative. Women in their thirties might be observed for a longer period of time anticipating a spontaneous cure. Metrorrhagia is thought by many to be a more ominous type of bleeding than is menorrhagia. Any lesion of the cervix, regardless of how benign it looks, should be biopsied.

The postmenopausal patient receiving estrogen therapy who suddenly bleeds should be advised to discontinue the hormone therapy. Bleeding will cease within a few days if due to the hormone therapy. If bleeding persists more than 10 days after hormones have been stopped, diagnostic curettage is mandatory. The intervening 10 days of waiting may be made partially reassuring by taking Papanicolaou smears or an endometrial biopsy. The physician must recognize that Papanicolaou vaginal smears are often apt to miss a carcinoma of the endometrium, and he must not be lulled into a false sense of security by negative smears. Occasionally a patient presents herself with widely isolated episodes of abnormal bleeding, occurring perhaps several months apart. The lack of persistence of symptoms is reassuring except, of course, in the menopausal years. In the last analysis curettage is indicated when persistence of abnormal uterine bleeding makes pathologic diagnosis necessary. It is a minor operation requiring a very short period of hospitalization, and when properly performed provides an authoritative answer

to the question of why the patient was bleeding. Concurrent biopsy of the cervix should also be done rewarding the careful surgeon with the occasional discovery of an unsuspected intraepithelial carcinoma of the cervix.

With the histologic findings of proliferative, secretory, or atrophic endometrium or of cystic glandular hyperplasia nothing further need be done. A microscopic diagnosis of adenomatous hyperplasia of the endometrium from a competent pathologist may warrant the performance of total hysterectomy since this lesion has been shown to be occasionally precancerous. The clinician should be well aware of the fact that pathologic evaluation of this type of hyperplasia is difficult. The great probability is that the curettage will produce an immediate cure of the complaint.

Persistent or recurrent dysfunctional bleeding from nonhyperplastic endometrium after curettage. Of 104 patients with normal (i.e., nonhyperplastic) endometrium who had persistent or recurrent uterine bleeding following curettage, bleeding stopped spontaneously in 26 and after hormone therapy in 7. One should not be too eager to intervene therefore in this group without allowing time for spontaneous cure; the period of time permitted would depend on whether the curettage had been done recently or at some considerable time in the past.

When surgical reintervention becomes necessary, since the chance of the second curettage producing a cure is good (60 per cent in this series), repeat curettage is the treatment of choice for recurrent dysfunctional uterine bleeding from nonhyperplastic endometrium in women of premenopausal age.

Those women in the menopausal years who have abnormal uterine bleeding have been shown by Randall and Corscaden and associates to have roughly a 3 times greater possibility of developing endometrial adenocarcinoma in later years than women who have a normal menopause. It is difficult, therefore, to criticize hysterectomy for recurrent or persistent uterine bleeding in this age group, particularly if a recent curettage has been unsuccessful.

A patient who, following one curettage with benign nonhyperplastic endometrium, has recurrent postmenopausal uterine bleeding should probably have a hysterectomy performed unless a medical contraindication to surgery exists.

There can be little disagreement that hysterectomy is indicated for persistently recurrent dysfunctional bleeding in women over 40 years old who have already had two curettages. If the patient is a poor surgical risk, radiation castration may be elected. If this same situation is encountered in an individual young enough so that hysterectomy would be undesirable, a third curettage should be done so that fertility might be preserved.

Persistent or recurrent dysfunctional uterine bleeding due to hyperplasia of the endometrium. As already stated, the precancerous possibility of adenomatous hyperplasia is significant enough to warrant hysterectomy once the diagnosis has been made rather than waiting for recurrent bleeding.

Recurrent bleeding due to cystic glandular hyperplasia makes hysterectomy indicated for several reasons. It is a persistently recurring disease. Fertility is very low once the disease has developed. Its relation to adenomatous hyperplasia is not clear and hence its precancerous relationship is not clear. The last reason makes hysterectomy preferable to radiation castration. In women under 40 years old, since a true precancerous status has not been proved, a second curettage may be elected rather than hysterectomy.

Hysterectomy versus radiation castration for recurrent nonhyperplastic bleeding. The advantage of radiation castration is, of course, the relative ease of applying radium or administering x-ray therapy, and this advantage is real if the patient is not a good surgical risk. However, the disadvantages of radiation castration are several. First of all, it is not always a permanent cure; there were 15 per cent

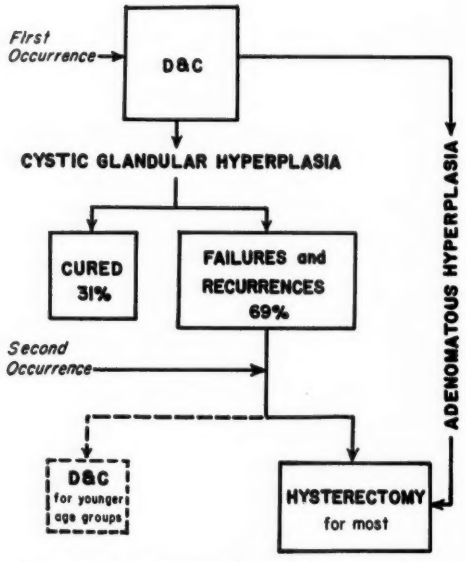


FIG. 6. The recommended surgical management of dysfunctional uterine bleeding due to hyperplasia of the endometrium.

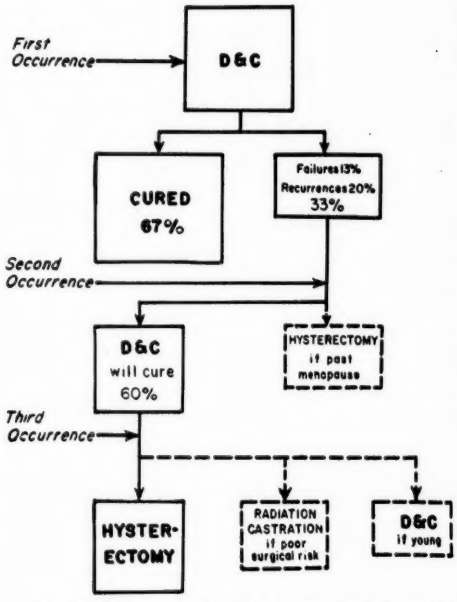


FIG. 7. Graph showing the recommended surgical management of nonhyperplastic dysfunctional uterine bleeding.

subsequent recurrences of bleeding in this series. Radiation castration destroys ovarian function producing menopausal symptoms while at hysterectomy one or both ovaries may be preserved. Radiation castration leaves a useless organ shown statistically to be more likely to develop endometrial cancer after an abnormal menopause. Radiation is certainly easier to administer and perhaps, therefore, is preferable under certain circumstances, such as in the smaller community where anesthesia and surgical facilities are not of superior caliber. However, where the best of surgical conditions are available, hysterectomy seems preferable to radiation except in cases of poor surgical risk.

We have attempted to portray our recommended management of dysfunctional uterine bleeding graphically in both Figures 6 and 7.

Hormone therapy. This study has been concerned with management of dysfunctional bleeding by curettage and other surgical procedures. The value of hormone therapy is questionable both for the hyperplasia and nonhyperplasia types of bleeding. Taylor (10) states that estrogens are "probably occasionally indicated" in functional uterine bleeding but points out the usually temporary character of the improvement resulting from their use; he states that "this cannot be regarded as the standard method of treatment of metrorrhagia because of the usual necessity of diagnostic curettage which may have a therapeutic value as well." Taylor also considers progesterone therapy "probably occasionally indicated" in endometrial hyperplasia.

In discussing endometrial hyperplasia Schröder (6) states that 50 per cent of menopausal women will be cured by dilatation and curettage and the remainder by radiation castration or vaginal hysterectomy. In younger women, difficulty is encountered in treatment and he calls attention to the fact

that follicular hormone or progesterone are successful now and then, "but are more frequently unsuccessful." In younger women he advises observation rather than radical procedures as long as no urgent indications such as blood loss with anemia exist; curettage is indicated in these patients with increasing bleeding. He also points out that hyperplasia might possibly cease spontaneously.

SUMMARY AND CONCLUSIONS

The causes of dysfunctional uterine bleeding are not evident histologically. Failure to ovulate may produce abnormal bleeding. The great majority of patients have normal endometrium while about 16 per cent have hyperplasia of the endometrium, usually cystic glandular in type and occasionally adenomatous. Anemia is infrequent as is thyroid dysfunction.

Fertility is normal before and after the occurrence of dysfunctional bleeding except in cases due to hyperplasia in which fertility is normal before the occurrence of dysfunctional bleeding but markedly diminished afterward.

In this series of 464 cases of dysfunctional bleeding initial surgical therapy consisted of dilatation and curettage in 83 per cent, dilatation and curettage with radium in 13 per cent, and hysterectomy in 4 per cent. We believe hysterectomy should rarely, if ever, be selected as the initial method of surgical treatment.

Curettage is preferred, the initial treatment being usually therapeutic as well as diagnostic.

Curettage by itself produced prompt cure of bleeding in 72 per cent of hyperplasia patients and in 87 per cent of nonhyperplasia patients. Dilatation and curettage with radium or x-ray was 100 per cent effective in producing immediate cure in both types of patients. Subsequent recurrence of bleeding months or years later occurred in both the hyperplasia and the nonhyperplasia groups but twice as frequently in the former; there were later recurrences of bleeding in both the curettage-radiation group as well as in the group that was treated by curettage alone.

Our recommendations for the surgical management of dysfunctional uterine bleeding are summarized graphically in Figures 6 and 7. The initial treatment of cystic glandular hyperplasia is curettage. Recurrent bleeding from cystic glandular hyperplasia may be treated by hysterectomy in view of the markedly diminished fertility rate associated with this disease; the exception would be a young woman who should be treated conservatively. The obscure relation between cystic glandular hyperplasia and adenomatous hyperplasia, the latter occasionally a precancerous disease, makes hysterectomy preferable to radiation castration. Hysterectomy is indicated once a diagnosis of adenomatous hyperplasia is made, but attention is called to the frequent disagreement in the diagnosis of this pathologic entity.

Bleeding from nonhyperplastic endometrium should initially be treated by curettage. Also, in the event of recurrence of bleeding after the first curettage, curettage should be repeated in view of the high incidence of cure of bleeding after the second curettage. If the recurrence of bleeding after the first curettage is early, one may even delay doing the second curettage for a time; a considerable number of spontaneous cures takes place under these conditions. For the third occurrence of persistent dysfunctional uterine bleeding hysterectomy is indicated in the older age groups; radiation castration may be substituted for hysterectomy if the patient is a poor surgical risk. In women young enough to warrant preservation of fertility, still a third curettage may be indicated.

REFERENCES

1. CORSCADEN, J. A., FERTIG, J., and GUSBERG, S. B. Carcinoma subsequent to the radiotherapeutic menopause. Am. J. Obst., 1946, 51: 1.
2. GUSBERG, S. B., MOORE, D. B., and MARTIN, F. Precursors of corpus cancer. Am. J. Obst., 1954, 68: 1472.
3. HECHTER, O., LEV, M., and SOSKIN, S. Relation of

hyperemia to action of estrin. Endocrinology, 1940, 26: 73-79.
4. Randall, C. L. Recognition and management of women predisposed to uterine adenocarcinoma. J. Am. M. Ass., 1945, 127: 20.
5. Schröder, R. Arch. Gyn. Berl., 1915, 104: 27.
6. Schröder, Robert. Endometrial hyperplasia in relation to genital function. Am. J. Obst., 1954, 68: 294-309.
7. Soskin, S., Wachtel, H., and Hechter, O. Treatment of delayed menstruation with prostigimine; therapeutic test for early pregnancy. J. Am. M. Ass., 1940, 114: 2090-2091.
8. Speert, H. A report on the premalignant phase of endometrial carcinoma. Cancer, N. Y., 1952, 5: 927-944.
9. Taylor, H. C., Jr. Endometrial hyperplasia and carcinoma of the body of the uterus. Am. J. Obst., 1932, 23: 309.
10. Idem. Endocrine therapy in gynecology and obstetrics; indications and limitations. J. Nat. M. Ass., 1954, 46: 7-13.
11. Te Linde, R. W., Jones, H. W., and Galvin, G. A. What are the earliest endometrial changes to justify a diagnosis of endometrial cancer? Am. J. Obst., 1953, 66: 953.

THE ACUTE EFFECTS OF COMPLETE HEART BLOCK ON THE PULMONARY CIRCULATION

ALBERT MOWLEM, M.D., and GILBERT S. CAMPBELL, M.D., Ph.D., Minneapolis, Minnesota

In 1949 Campbell, Haddy, Adams, and Visscher (1) produced pulmonary edema in dogs by raising the intracranial pressures in these animals. They showed that increased intracranial pressure resulted in bradycardia, lowering of the cardiac output, moderate increase in mean pulmonary artery pressure, and marked elevation of mean pulmonary vein pressure. The degree of pulmonary edema was correlated with the height and duration of the elevated pulmonary vein (and by inference "capillary") pressure. These investigators suggested that perhaps centrally induced increase in the peripheral resistance played a role in this process. That some of the responses were mediated by increased vagal tone was indicated by the fact that the observed changes were prevented or reversed by cervical vagotomy or the administration of atropine. It was demonstrated later by Campbell and associates (2) that bradycardia induced in dogs by vagal stimulation or acetylcholine also resulted in elevation of the pulmonary venous pressures. Harrison and Liebow confirmed that increasing intracranial pressure in dogs resulted in bradycardia and occasional pulmonary edema, the latter occurring especially when the left atrial pressure rise was not transitory but remained elevated for more than 15 minutes.

Sarnoff and Sarnoff (6) on the other hand produced pulmonary edema in dogs and rabbits by injecting fibrin into the cisterna magna of these animals. They demonstrated that an increase in peripheral vascular resistance as well as constriction of the peripheral vascular bed of these animals resulted in an increase in the volume of blood and elevation of the vascular pressures within the lesser circulation with subsequent development of pulmonary edema.

Since earlier studies on the association of bradycardia and pulmonary edema were produced by cerebrally induced bradycardia, the present investigation was carried out whereby bradycardia was produced by surgical heart block, as by Taufic and Starzl and their associates, and was therefore free from direct cerebral effects on peripheral vascular resistance.

MATERIALS AND METHODS

Observations were made before and after production of heart block in mongrel dogs. Initially, a right thoracotomy was performed on dogs anesthetized with sodium pentothal (35 mgm./kgm. of body weight) and receiving oxygen under positive pressure by means of an endotracheal tube. The azygos vein was then divided and ligated following which the left atrium (L. A.) of the heart was partially dissected from the posterior aspect of the superior vena cava and the right atrium so that a polyethylene catheter suitable for measuring pressures and obtaining blood samples could be inserted into it. Similarly another polyethylene catheter was inserted into the pulmonary artery (P. A.) from the right ventricle. Both catheters were brought out through the anterior chest wall near the midline in such a manner as not to interfere with the expansion of the right lung when the chest was closed. Following closure of the chest, the dogs were allowed to resume breathing on their own and come to a steady state after

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

This investigation was supported in part by Research Grant H-1784C from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and the Graduate School of the University of Minnesota.

Dr. Mowlem is an American Cancer Society Clinical Fellow in Surgery.

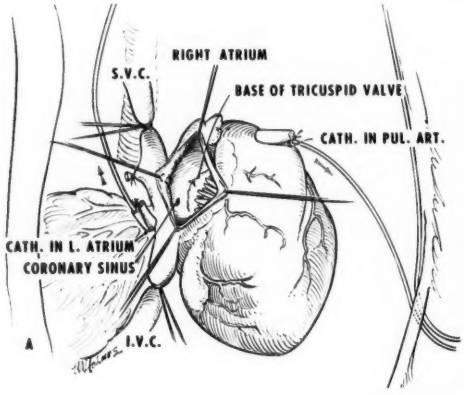


FIG. 1. Technique of surgical production of heart block. A, Right atrium opened under inflow stasis showing suture at base of posterior leaflet of tricuspid valve. B, Atriotomy closed L.A. and P.A. catheters shown in place.

which they were connected via the endotracheal tube to a closed system spirometer containing 100 per cent oxygen. In this manner oxygen consumption was obtained and cardiac output calculated by the direct Fick method using oxygen consumption and differences in oxygen content of mixed venous (P. A.) and arterial (L. A.) blood samples. Oxygen content in blood was determined by the method of Van Slyke and Neill. Simultaneous integrated mean pressure readings were obtained using Statham strain gauge blood pressure manometers (transducers) from the P. A., the L. A., and femoral artery (F. A.) catheters when the chest was open, as well as during the measurement of the cardiac output following closure of the chest.

After the initial observations were made, the right side of the chest was reopened and heart block produced under direct vision by opening the right atrium and suturing the atrioventricular bundle of His under inflow stasis as described by Taufic and Starzl and their associates (see Fig. 1), care being taken to replace all the blood lost during the procedure. Immediately following the block (2 to 5 minutes) and with the chest still open,

TABLE I.—ACUTE VASCULAR EFFECTS AFTER HEART BLOCK IN DOGS

				Mean L.A. pressure (mm.Hg)				*Mean P.A. pressure (mm.Hg)*			
				Open chest		*Closed chest*		*Open chest*		*Closed chest*	
Exper. No.	*C.O., per cent*	*Pulse, per cent*	*Mean F.A. pr., per cent*	*Preblock*	*2–5 min. after block*	*Preblock*	*1 hour after block*	*Preblock*	*2–5 min. after block*	*Preblock*	*1 hour after block*
1	84	60	—	—	—	3.5	2.5	—	—	—	—
2	62	61	91	—	—	5.0	10.0	—	—	—	—
3	50	52	67	5.0	13.5	5.0	7.0	—	—	—	—
4	40	34	86	2.5	13.0	0.5	2.5	—	—	—	—
5	49	46	88	−1.0	16.0	1.5	2.5	—	—	—	—
6	51	57	78	—	25.0	6.5	16.0	—	—	—	—
7	73	53	—	8.5	12.5	—	6.5	—	—	—	—
8	60	62	88	8.0	12.0	3.0	8.0	—	—	—	—
9	87	47	85	10.0	15.5	6.5	3.0	—	—	—	—
10	53	45	78	6.5	9.0	6.5	8.5	15.0	17.5	15.0	15.0
11	59	35	73	7.0	5.0	1.0	3.0	15.0	10.0	10.0	5.0
12	31	20	60	4.5	—	8.0	0.5	15.0	—	2.0	0.0
13	71	54	95	3.0	2.5	2.5	0.0	12.5	9.5	10.0	0.0
14	46	43	91	6.0	7.5	0.0	0.0	9.0	20.0	8.5	15.0
15	—	40	—	4.0	17.5	2.0	—	16.0	20.0	17.5	—
16	57	45	72	8.0	16.0	5.0	7.0	20.0	22.0	13.5	17.5
17	73	57	83	5.5	17.0	3.0	4.0	21.5	23.0	15.0	17.5
Average	73	48	82	6.4	13.0	3.7	5.1	15.5	17.4	11.4	10.0

C.O., cardiac output. Pulse, mean F.A. (femoral artery) pressure given in per cent of preblock values.
L.A., left atrim; P.A., pulmonary artery.

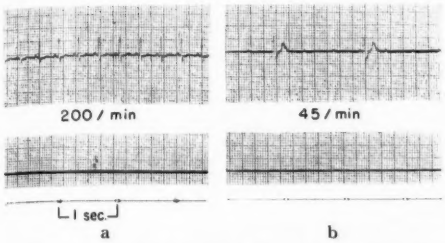


FIG. 2. Illustrative example of electrocardiographic tracing before and after production of surgical heart block. a, Lead III before block, heart rate 200 per minute; b, Lead III after complete heart block, heart rate of 45 per minute.

the previous pressure measurements (P. A., L. A., F. A.) were again obtained and also repeated after the chest was closed for the second time followed by remeasurement of the cardiac output.

It should be pointed out here that intrathoracic pressure after the chest was closed was maintained at subatmospheric levels by means of a chest catheter connected to −12 centimeter of water suction. Heart rates and evidence of heart block were obtained from electrocardiographic tracings (Fig. 2). It was not possible to obtain heart block in all the dogs so operated upon. Heart block persisted in one-half of the animals and therefore only the results obtained from the persistent heart block group are considered.

RESULTS

The over-all results obtained in 17 cases of acute experimental heart block are summarized in Table I and illustrated in Figure 3.

Effects on cardiac output, pulse, and mean femoral artery pressure: The average cardiac output (C. O.) dropped to 59 per cent of the preblock value measured about 1 hour after the block was obtained. This drop occurred concomitantly with a bradycardia of 48 per cent of the initial rate. It will be noted from the individual experiments that the magnitude of the drop in the C. O. is roughly related to the degree of drop in heart rate, i.e., the lower the drop in heart rate the lower the C. O. For example, in experiment

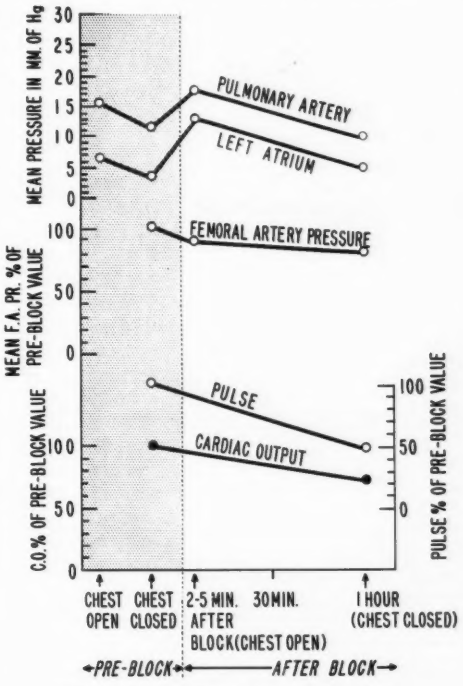


FIG. 3. Acute effects of heart block in dogs.

12 when the pulse rate dropped to 20 per cent of the initial rate, the cardiac output decreased to 31 per cent, whereas in experiment 8, a bradycardia of 62 per cent was associated with a C. O. of 60 per cent. The systemic mean arterial pressure as measured in the femoral artery also dropped slightly (average 82 per cent preblock value) following heart block. This was not related to blood loss from the operative procedure since blood loss was replaced.

Effects on mean left atrial and pulmonary artery pressures: As will be seen from Table I, there was an over-all twofold rise in the average mean L. A. pressure from 6.4 to 13 millimeters of mercury within 2 to 5 minutes after the block was obtained and while the chest was still open. This rise was not long-lasting, for the final pressure (5.1 mm. Hg) dropped almost down to its original level (3.7 mm. Hg) by the time the chest

was closed, i.e., about 1 hour following the block. This immediate rise in the left atrial pressure was exhibited in 14 out of 17 dogs (82 per cent of the cases). During the early experiments the pulmonary artery pressure was not measured, however, this was obtained in the last 8 dogs. In these cases observation indicates that although there was rise in the average mean pulmonary artery pressure immediately after the block (from 15.5 to 17.4 mm. Hg) this was slight and probably not significant.

DISCUSSION

No pulmonary edema was observed in these experiments since the left atrial pressure elevation was mild and transitory. Yet, in cerebral trauma studies, such edema was noted when a marked and sustained elevation of left atrial pressure occurred.

It has been suggested by Sarnoff (6) that peripheral vasoconstriction in the cerebral trauma studies would tend to shift blood from the systemic to the pulmonary circulation with subsequent elevation in L. A. pressure and the appearance of pulmonary edema. In their studies systemic blood pressure rose in spite of a drop in cardiac output, indicating a marked systemic vasoconstriction.

In the present investigation, the initial rise in L. A. pressure may be a reflection of a relative failure in cardiac function (left ventricle) immediately following induction of heart block. Furthermore, in our studies, systemic vasoconstriction was unable to maintain normal systemic blood pressure as cardiac output fell. Perhaps the absence of marked systemic vasoconstriction in these studies prevented the shift of blood from the systemic to the pulmonary vascular bed and accounts in part for the transitory elevation in L. A. pressure. Another factor may be the "stress relaxation" phenomenon described by Sarnoff and Berglund (5) wherein the isolated, perfused pulmonary vascular bed accommodated successively higher flows with only transitory elevations in pulmonary vascular pressures.

Studies are now in progress to produce heart block and to administer pharmacologic agents to increase or decrease the peripheral vascular resistance in dogs in order to observe the resultant effects on the L. A. pressure.

SUMMARY

1. The acute effects of surgically induced heart block on the cardiac output, the systemic arterial pressure and the pressures within the lesser (pulmonary) circulation in dogs are described in this study.

2. There was an initial prompt rise in the left atrial pressure but this dropped back down to normal within about 1 hour. There was an initial and sustained drop in cardiac output, heart rate, and peripheral arterial pressure.

3. The significance of the rise in left atrial pressure and its subsequent return to normal is discussed in the light of other experimental work relative to production of pulmonary edema in the laboratory.

REFERENCES

1. Campbell, G. S., Haddy, F. J., Adams, W. L., and Visscher, M.B. Circulatory changes and pulmonary lesions in dogs following increased intracranial pressure and the effect of atropine on such changes. Am. J. Physiol., 1949, 158: 98.
2. Campbell, G. S., Haddy, F. J., and Visscher, M. B. Effect of acute bradycardia in pulmonary vascular pressures in anesthetized dogs. Proc. Soc. Exp. Biol., N. Y., 1949, 71: 52.
3. Fick, A. In Grollman, A.: The Cardiac Output of Man in Health and Disease. Springfield: Charles C Thomas, 1932.
4. Harrison, W., and Liebow, A. A. The effects of increased intracranial pressure on the pulmonary circulation in relation to pulmonary edema. Circulation, 1952, 5: 824.
5. Sarnoff, S. J., and Berglund, E. Pressure-volume characteristics and stress relaxation in the pulmonary vascular beds of dogs. Am. J. Physiol., 1952, 171: 238.
6. Sarnoff, S. J., and Sarnoff, L. C. Neurohemodynamics of pulmonary edema—injection of fibrin into the cisterna magna of dogs and rabbits. Circulation, 1952, 6: 51.
7. Starzl, T. E., Gaertner, R. A., and Baker, R. R. Acute complete heart block in dogs. Circulation, 1956, 12: 82.
8. Taufic, M., Bashour, F. A., and Lewis, F. J. Production of heart block in dogs under direct vision. Surgical Forum 1954; American College of Surgeons. P. 96. Philadelphia and London: W. B. Saunders Co., 1955.
9. Van Slyke, D. D., and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem., 1924, 61: 523.

EFFECTS OF THE SECRETIONS OF THE STOMACH, DUODENUM, JEJUNUM, AND COLON ON THE ESOPHAGUS OF THE DOG

S. F. REDO, M.D., and W. A. BARNES, M.D., New York, New York

RESTORATION OF CONTINUITY between the esophagus and stomach following resection of the esophagus or cardia for benign or malignant conditions has been accomplished by direct anastomosis of the esophagus to the stomach or by interposition of segments of jejunum, ileum, or colon. Plastic tubing also has been used to bridge the gap between esophagus and stomach. Following esophagogastrostomy, esophagitis or peptic ulceration of the esophagus with bleeding or stricture formation frequently occurs. The interposition of an adequate length of jejunum or colon is designed to prevent reflux of gastric juice into the esophagus and thereby avoid these complications.

The effect on the esophagus of gastric mucosa implanted into that organ is well known. The effects of secretions of the jejunum, colon, duodenum, and of combined gastroduodenal fluids on the esophagus have not been as well documented. Since different segments of the gastrointestinal tract have been used to restore continuity following resection of the esophagus or cardia, it seemed desirable to determine and correlate in one study the effect of their secretions on the esophagus.

MATERIALS AND METHODS

Mongrel dogs weighing from 9 to 23 kilograms were anesthetized with intravenous nembutal. Oxygen was administered through an endotracheal tube connected to an automatic respirator. Through a left thoracotomy the esophagus was elevated by means of 2 stay sutures placed approximately 6 and 12 centimeters above the diaphragm. The appropriate segment of the gastrointestinal tract was drawn up into the chest through an opening in the diaphragm and anastomosed in end-to-side fashion to the esophagus between the stay sutures. Sutures of cotton were used throughout.

During the operation all dogs received an infusion of 5 per cent dextrose in water with terramycin (250 mgm.). Oral fluids were begun on the first postoperative day and most of the dogs were on full kennel feedings by the fourth day after operation. A few received injections of penicillin and dihydrostreptomycin for 1 or 2 days postoperatively.

The esophagus and the implanted portion of gastrointestinal tract were examined grossly and microscopically. The specimens were fixed in 10 per cent formalin, sectioned, and stained with hematoxylin and eosin.

Five groups of dogs were prepared.

Group I: Gastric tube implant. In these animals clamps were placed longitudinally along the greater curvature of the stomach from the antrum to the fundus. The stomach was incised between the clamps. The greater curvature portion was then closed to form a tube with an open end at the pyloric region (isoperistaltic). The remainder of the stomach was closed along the line of division. The gastric tube was anastomosed to the esophagus in an isoperistaltic manner as described before (Fig. 1).

Group II: Duodenal tube implant. The duodenum was divided near the pylorus and also distal to the entrance of the common bile and pancreatic ducts. The proximal end of

From the Department of Surgery of the New York Hospital and Cornell University Medical College.
Aided by a grant (RG-4299) from the United States Public Health Service.

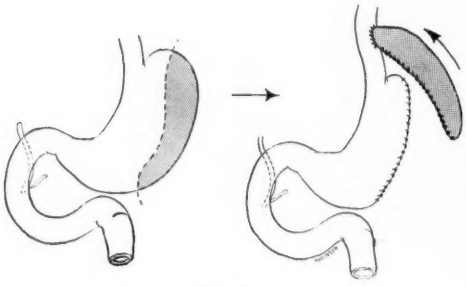


FIG. 1.

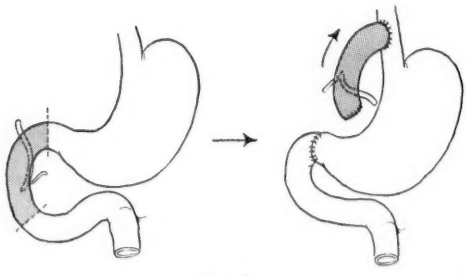


FIG. 2.

FIG. 1. Gastric tube implant. A tube formed from the greater curvature of the stomach is anastomosed to the esophagus in isoperistaltic fashion.

FIG. 2. Duodenal tube implant. A segment of duodenum containing the entrance of the bile and pancreatic ducts is isolated. The proximal end is closed; the distal end is anastomosed isoperistaltically to the esophagus.

FIG. 3. Gastroduodenal tube implant. The stomach is transected in the middle third and the duodenum divided distal to the entrance of the bile and pancreatic ducts. The gastric end is closed and the duodenal end anastomosed to the esophagus in isoperistaltic manner.

FIG. 4. Jejunal tube implant. A segment of jejunum is isolated 10 centimeters from the ligament of Treitz. The proximal end is closed and the tube anastomosed to the esophagus in isoperistaltic fashion.

FIG. 5. Colonic tube implant. A segment of transverse colon is isolated. The proximal end is closed and the tube anastomosed to the esophagus in isoperistaltic fashion.

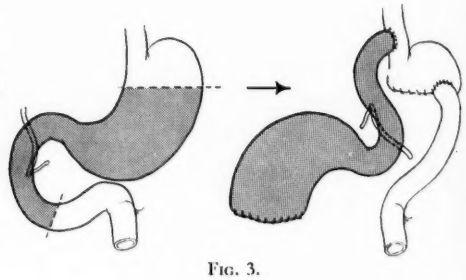


FIG. 3.

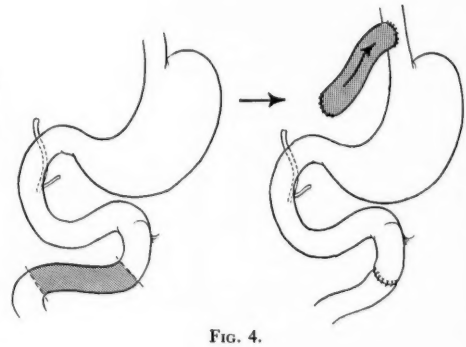


FIG. 4.

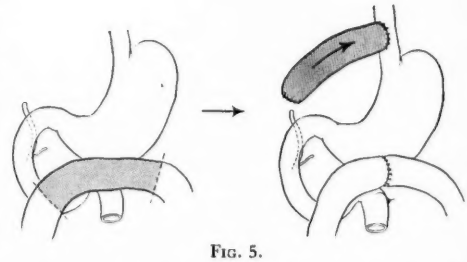


FIG. 5.

the segment was closed. The distal end was anastomosed to the lower esophagus in isoperistaltic, end-to-side fashion. Gastrointestinal continuity was restored by performing end-to-end gastroduodenostomy (Fig. 2).

Group III: Gastroduodenal tube implant. A gastroduodenal tube was created by transecting the stomach somewhere in the middle third and the duodenum was divided distal to the entrance of the common bile and pancreatic ducts. The gastric end of the segment was closed and the duodenal end was anastomosed to the esophagus. A gastroduodenostomy restored gastrointestinal continuity (Fig. 3).

Group IV: Jejunal tube implant. A segment of jejunum 10 to 15 centimeters in length was isolated 10 centimeters from the ligament of Treitz. The proximal end was closed and the tube anastomosed to the

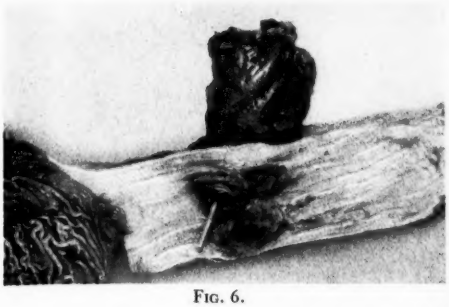


FIG. 6.

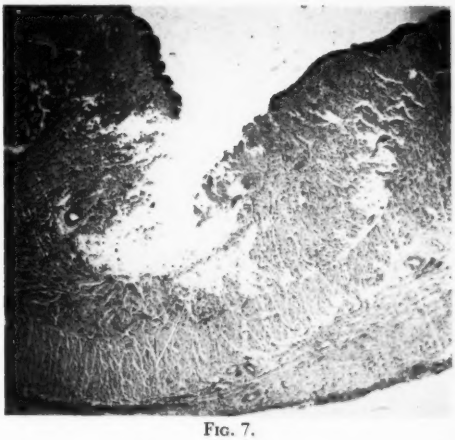


FIG. 7.

FIG. 6. Gastric tube 91 days after operation. Two large ulcers are present in the esophagus.

FIG. 7. Microscopic appearance of ulcer shown in Figure 6. It extends deep into the muscularis. ×9.

esophagus. Intestinal continuity was restored by end-to-end jejunojejunostomy (Fig. 4).

Group V: Colon tube implant. These dogs were fed clear fluids and neomycin for 2 days prior to operation. A segment of transverse colon 10 to 15 centimeters in length was isolated, the proximal end closed, and the tube anastomosed to the esophagus. Continuity of the colon was established by end-to-end anastomosis (Fig. 5).

RESULTS

Thirty-two dogs were subjected to operation. In Table I are summarized the effects on the esophagus of the secretions of these various portions of the gastrointestinal tract.

Group I. Five dogs were prepared. One died on the tenth postoperative day. The others were killed 16, 36, 53, and 91 days after operation. In all there were deep penetrating ulcers opposite or just distal to the site of anastomosis of the gastric tube to the esophagus (Figs. 6 and 7).

Group II. Eleven animals were prepared. Eight died 2 to 3 days after operation and 1 died on the eighth day. Two were killed 20 and 144 days postoperatively. All animals developed superficial, linear esophagitis extending through the mucosa in some areas but not accompanied by a conspicuous inflammatory cellular response. There were no deep, penetrating ulcers (Figs. 8 and 9).

Group III. Of 5 dogs prepared 2 died on the first postoperative day. The others were killed 41, 56, and 91 days after operation. In all animals superficial, linear esophagitis occurred without deep ulceration. There was little microscopic evidence of inflammation (Figs. 10 and 11).

Group IV. Of the 7 dogs in this group, 3

TABLE I.—EFFECTS OF SECRETIONS OF VARIOUS PORTIONS OF THE GASTROINTESTINAL TRACT ON THE ESOPHAGUS

Implant of	*No. of dogs*	*Died or killed, days postop.*	*Findings*
Stomach	5	D 10 K 16, 36, 53, 91	Penetrating ulcers of esophagus in all
Duodenum	11	D 2, 2, 2, 2, 2, 2, 2, 3, 8 K 20, 144	Superficial, linear esophagitis in all. No deep ulcers
Stomach and duodenum	5	D 1, 1 K 41, 91, 56	Prominent linear esophagitis. No deep ulcers
Jejunum	7	D 1, 2, 5, 10, 14 K 61, 119	Minimal roughening of mucosa. No esophagitis or ulcers
Colon	4	D 5 K 19, 73, 89	Mucosa unremarkable. No esophagitis or ulcers

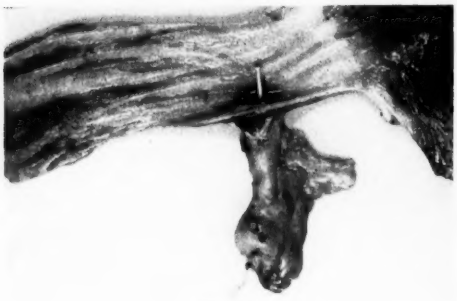


FIG. 8.

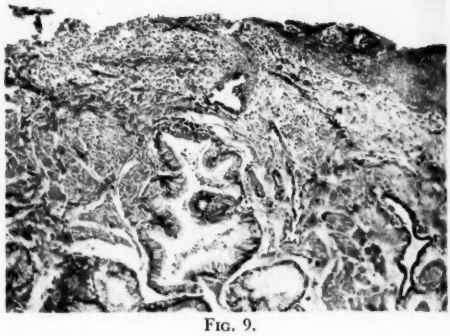


FIG. 9.

FIG. 10.

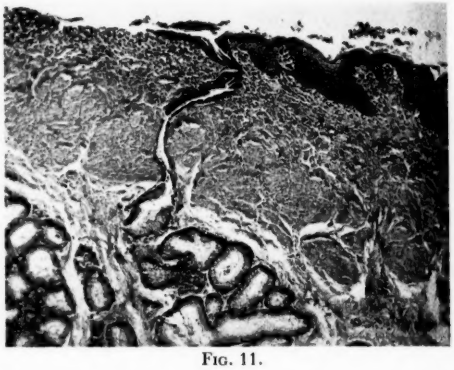


FIG. 11.

FIG. 8. Duodenal tube 146 days after operation. The esophagus has a markedly corrugated appearance with superficial linear erosions. There are no penetrating ulcers.

FIG. 9. Microscopic appearance of esophagus shown in Figure 8. There is superficial erosion with slight inflammatory response. ×7.

FIG. 10. Gastroduodenal tube 91 days after operation. There is superficial linear esophagitis without ulceration.

FIG. 11. Microscopic appearance of esophagus shown in Figure 10. There is erosion into the submucosa similar to that seen with duodenal tube implants. ×8.

died on the first to fifth day after operation, 1 died on the tenth day and 1 on the fourteenth day. Two were killed 61 and 119 days after operation. In all dogs minimal linear esophagitis was found without gross ulceration (Fig. 12), and only minimal cellular inflammatory response was evident on microscopic examination (Fig. 13).

Group V. Of the 4 animals in this group, 1 died on the fifth day after operation. The others were killed 19, 73, and 89 days after surgery. Grossly, the esophagus appeared normal (Fig. 14). Microscopically, the esophagus showed only minimal inflammatory changes (Fig. 15).

DISCUSSION

These studies indicate the conspicuous differences in the effects on the canine esophagus of gastric juice as compared with duodenal contents and secretions of the jejunum and colon. In dogs in which the esophagus was bathed with a continuous flow of gastric juice (group I) deep penetrating ulcers developed. The animals in which the gastric juice bathing the esophagus was mixed with duodenal secretions (group III) showed linear esophagitis with changes in the mucosa only. This response resembled closely that noted in the dogs with a duodenal implant (group II) in which the esophagus was bathed with bile and pancreatic secretions only. Those dogs in which tubes of jejunum or colon were implanted into the esophagus (groups IV and V) revealed minimal or no superficial linear esophagitis. In none, except those in which a gastric tube was implanted into the esopha-

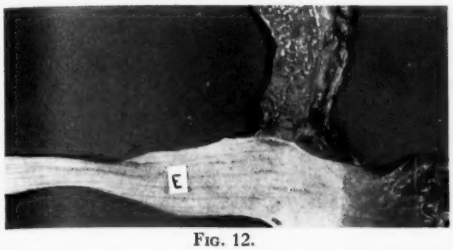


FIG. 12.

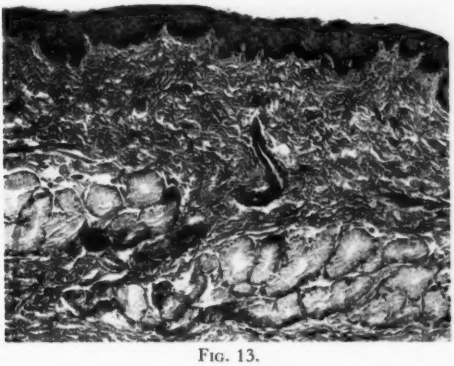


FIG. 13.

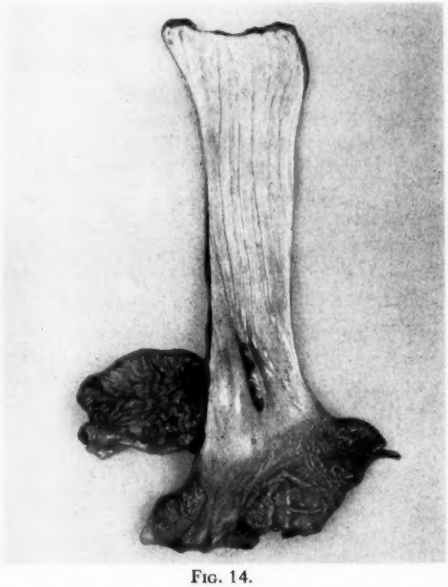


FIG. 14.

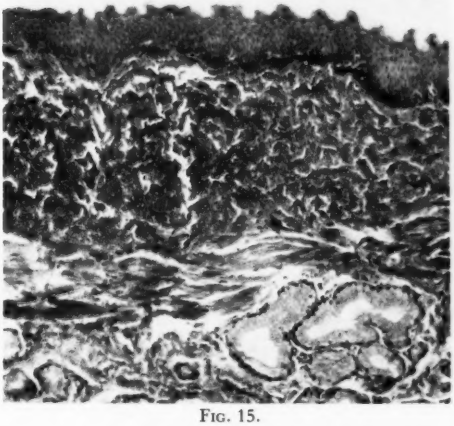


FIG. 15.

FIG. 12. Jejunal tube 119 days after operation. Superficial mucosal irregularity is barely recognizable. The small dark area in the esophagus is artefact.

FIG. 13. Microscopic appearance of the esophagus shown in Figure 12. The mucosa is intact without evidence of ulceration. ×14.

FIG. 14. Colonic implant 89 days after operation is illustrated. There is no abnormality evident in the esophagus.

FIG. 15. Microscopic appearance of the esophagus shown in Figure 14. The mucosa is intact without evidence of ulceration. ×16.

gus, was there marked inflammatory response or did deep ulcers form.

Ripley and associates implanted Heidenhain pouches into the esophagus of dogs and found that severe ulcerative esophagitis developed early in the postoperative period. Battersby reported on the use of ileum and ascending colon to replace a segment of the esophagus. No mention is made of follow-up studies regarding the development of esophagitis.

We noted previously (2) that mild linear esophagitis occurred in only 1 of 17 dogs subjected to resection of the esophagogastric junction and esophagojejunostomy in Roux-Y fashion. In this dog the jejunojejunostomy was only 5 centimeters from the esophagojejunostomy stoma.

The results indicate that penetrating ulcers accompanied by a marked inflammatory response that may result in perforation occur when unaltered acid-pepsin juices are

in contact with the esophagus in the dog. When gastric juice mixed with duodenal contents, or when bile and pancreatic secretions, bathe the esophagus, only linear superficial esophagitis without deep ulcers or marked inflammatory response results. The secretions of jejunum or colon produce little or no change in the esophagus.

In humans it is recognized that the regurgitation of unaltered gastric juice may lead to the formation of peptic ulcer in the esophagus often with bleeding, perforation, or stricture.

After total gastrectomy in patients who have an esophagoduodenostomy or esophagojejunostomy, mild, linear esophagitis may develop, characterized by shallow mucosal erosions without deep penetration or prominent inflammatory response. This type of reaction would appear less likely to give rise to serious sequelae such as perforation, stricture, or bleeding.

The importance of preventing regurgitation of gastric juice into the esophagus is reemphasized by these findings. In dealing with lesions of the esophagus or cardia of the stomach surgical procedures should be planned to prevent regurgitation of unaltered gastric contents. This may be accomplished by esophagojejunostomy in Roux-Y fashion or by inserting a segment of jejunum or colon between the esophagus and stomach.

SUMMARY

Dogs were prepared so that secretions of the stomach or duodenum, jejunum, and colon constantly bathed the esophagus. When the esophagus was bathed with unaltered gastric juice, deep penetrating ulcers developed. When gastric juice mixed with duodenal contents, or duodenal contents alone, were in constant contact with the esophagus, only a superficial, linear esophagitis developed. Secretions of the jejunum or colon produced minimal or no change in the esophagus.

CONCLUSIONS

Operations that permit unaltered gastric contents to enter the esophagus are to be avoided since esophagitis and ulceration may follow. Operations in which gastric juice mixed with duodenal secretions, or duodenal secretions alone, enter the esophagus are less likely to be associated with serious degrees of esophagitis and its complications. Secretions of jejunum or colon produce minimal or no change in the esophagus, hence these organs may be of value in the restoration of continuity of the intestinal tract following resection of the esophagogastric junction.

REFERENCES

1. Battersby, J. S. Esophageal replacement by use of the right colon. Surgical Forum 1952; American College of Surgeons. P. 279. Philadelphia and London: W. B. Saunders Co., 1953.
2. Redo, S. F., and Barnes, W. A. Morphologic and physiologic studies on the gastric remnant following resection of the esophago-gastric junction and esophago-jejunostomy. Surg. Gyn. Obst., 1954, 99: 310.
3. Ripley, H. R., Leary, W. V., Grindlay, J. H., Seybold, W. D., and Code, C. F. Experimental studies of peptic ulceration and stricture of the lower part of the esophagus. Surgical Forum 1950; American College of Surgeons. P. 60. Philadelphia and London: W. B. Saunders Co., 1951.

GENERAL PRINCIPLES OF FRACTURE MANAGEMENT IN THE AGED

EDGAR M. BICK, M.D., F.A.C.S., New York, New York

THE POPULATION of the city of New York in 1956 included 700,000 persons more than 65 years old. It has been estimated that by 1960 there will be 15 million residents of the United States in that age group. This enormous population with its special problems in physiology, psychology, economics, and sociology requires and will require increasing attention from many agencies and professions. The high accident rate which has become a commonplace in modern living will demand a considerable proportion of this effort in the care of the traumas of the aged. In recognition of this growing problem, a series of over 500 fractures and dislocations occurring among the elderly was studied in order to gauge the relative advantages and disadvantages of current concepts of fracture therapy when applied to their special circumstances. Specific fractures will not be discussed separately in this survey on general management since detailed reports on several of the more common ones have been and continue to be published in current periodicals.

Table I expresses in order of frequency the wide distribution of fractures and dislocations in a group of 516 persons over the age of 60. Their division by age and sex suggests the statistical distribution of the type of cases which may be anticipated by any surgeon or agency having the care of similar populations. With 3 exceptions the distribution is more or less the same as would be found in any adult group. The exceptions, however, are important: the hip, the vertebra, and the shoulder. Together these 3 represent 58 per cent of the total. Fractures about the wrist which are third in numerical order would be equally high or higher in any general list. These represent another 14 per cent. The 3 exceptions also represent temporary total disabilities, and 2 of them, the hip and vertebra often represent permanent partial disabilities of significant degree.

Table II indicates that in this series fractures occur more frequently in females than in males. In those between the ages of 60 and 75 years the ratio is 3 to 1; in individuals over 75 years old the ratio of females to males is 11 to 1. The aged population of New York in 1956 showed an over-all ratio of 1.2 females to 1 male. One must therefore assume that elderly females are far more subject to fracture than are their male contemporaries. This fact may be due to greater daring on the part of the ladies or to greater brittleness of their skeletons. In either case the statistical fact may be of some interest to casualty companies and to institutions responsible for their medical supervision.

A study of this series of cases has elicited certain general observations which are sufficiently impressive to have earned at least the status of working hypotheses. Clinical study of this material does not lend itself either to experimental control or to precision measurement. As indicated in a previous article (1), in our present state of knowledge the fact that it is impossible to determine the actual healing point of a fracture at any age is too often ignored in attempts to estimate the time factor in bone union. However, within the limits of clinical observation it appears as though reparative osteogenesis in the aged occurs within a time span generally equal to that of adults of all ages. The quality of bone produced in the process is conditioned by the quality of the bone before fracture. Osteoporotic bone

From the Orthopaedic Service, The Mount Sinai Hospital, New York.

TABLE I.—DISTRIBUTION OF 516 CASES OF FRACTURES AND DISLOCATIONS IN PATIENTS OVER 60 YEARS OF AGE, TABULATED IN ORDER OF FREQUENCY BY AGE AND SEX (EXCLUDING PATHOLOGIC FRACTURES)

	Age, years, and sex																	
	60–64		*65–69*		*70–74*		*75–79*		*80–84*		*85–89*		*90–94*		*95–99*		*Total*		
Fracture site	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*Total*
Hip: Intracapsular	1	12	5	11	3	19	1	21	3	22		13		2			13	100	173
Intertrochanteric	1	2	4	2	1	7	1	12	1	14		12		2		1	8	52	
Vertebra	6	16	6	16	2	13	4	7	1	3		1					18	56	74
Radius-ulna (wrist)	3	20	7	12	1	9		7	1	9		3					12	60	72
Humerus (shoulder)	2	9	5	13	4	4	2	9		3		2					13	40	53
Foot and toes	5	8	1	6	1	8	1	3		4							8	29	37
Tibia-fibula (ankle)	3	8		5	1	3		4		1						1	4	22	26
Hand and fingers	1	3	1	3	5	1		2		2		1					7	12	19
Femur (shaft)	1		1			1		4		6							2	11	13
Pelvis		3	1			2			1	2							2	7	9
Shoulder (disloc.)		1	1	3	1			1		1							2	6	8
Humerus (shaft)	1	3						2				1					1	6	7
Clavicle		1		1	1	2								2			1	6	7
Ribs			3	1		1				1							3	3	6
Tibia-fibula (shaft)	1	1			1												2	1	3
Elbow (dislocation)		1	1			1											1	2	3
Patella				2		1												3	3
Radius-ulna (shaft)			1					1									1	1	2
Scapula								1										1	1

produces osteoporotic callus. Since the process of ossification proceeds regardless of the degree of calcification of trabecular matrix, x-ray films showing an apparent persistence of fracture lines in the presence of some degree of senile osteoporosis require rather experienced interpretation. Persistent relative radiolucence of a fracture line in a physically sound part may not indicate nonunion.

There are no techniques so far developed especially applicable to the treatment of fractures of the aged. There are only limitations of objectives conditioned by the limited strength and limited resiliency of their musculoskeletal tissues. In relation to fracture therapy this means first a greater need for a resting period between emergency care and definitive treatment. Manipulation or surgery is best performed after the patient has been allowed time for the recovery from the shock of trauma. This is generally true of all patients; it may be vital in the aged.

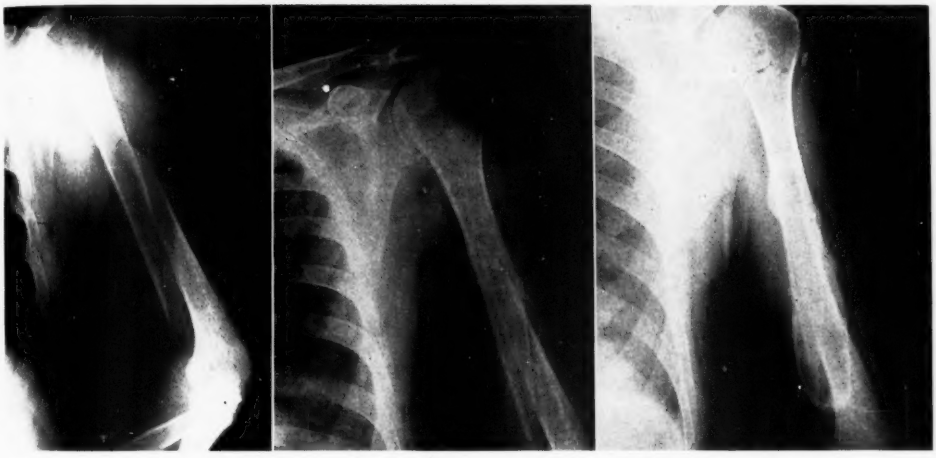
TABLE II.—RATIOS OF AGE AND SEX IN 516 AGED PATIENTS WITH FRACTURES

	Total	*Under 75*	*Over 75*
Male	98	82	16
Female	418	235	183
Ratio of male to female	1:4.3	1:2.9	1:11.4

Sex population ratio over 65 years of age in New York in 1956: male 322,000, female 386,000, ratio male to female 1:1.2.

A second limitation is the relative softness or compressibility of the bones. Aging bone will not withstand the internal pressures of screws, plates, or nails as readily as does more viable bone. Local erosion is more apt to allow loosening of the metal or its cutting through cortex. This is of course a variable factor and does not necessarily contraindicate the use of internal fixation. However, it should be understood that such procedures are less dependable in the aged than they are in other persons. For similar reasons forcible manipulation may destroy fracture surfaces to a degree more deforming than would occur if a less perfect, though adequate reduction were accepted. This too is a matter of judgment gained only by experience and cannot be quantitatively expressed.

A third limitation appears during the period of aftercare. Early return of function is of equal importance among the aged for both psychologic and economic reasons as in younger persons. However, one of the chief obstructions in the older groups, especially in the common fractures at or near the joints, is the normally decreased elasticity of the muscular and periarticular connective tissues. This decrease is histologically demonstrable. It implies easy postfracture



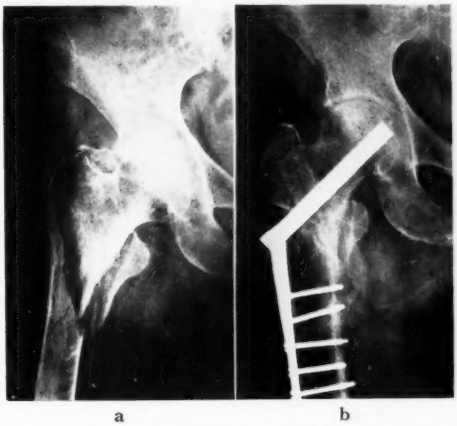
a b c

FIG. 1. a, Fracture of humerus in 76 year old male; b, 6 weeks after fracture, fully developing primary callus; c, 4 months after fracture, firm definitive callus.

strain of inelastic ligaments, capsules, and fascial planes. It becomes necessary, therefore, to temper the urge for early and rapid mobilization of the part by measures which to the tissues of an elderly person may cause excessive stretch. Often enthusiastic attempts at exercise or self-stretching of the affected area result in a pain-spasm sequence which retards rather than enhances mobility. A good rule in the management of postfracture rehabilitation of the aged is to encourage daily increased purposeful activity in place of the formal exercises now so fashionable in the younger adults.

It is common experience in the care of these patients that the recovery of reasonable mobility in shoulder fractures takes a much longer time than is generally anticipated. Let it. Attempts to accelerate the process by insisting on active exercise is not only apt to retard motion but causes an unnecessary persistence of pain. Daily practice in attempting the ordinary activities of the arm will probably be more successful. In dealing with fractures of the vertebrae graded daily walks among one's neighbors or in one's garden are apt to be more salubrious than exercises directed to the muscles of the trunk which, in respect to the vertebral and intervertebral degenerations inherent in the senescent spine, are more apt to stir up new aches than to improve existing ones. In recently healed fractures of the hip joint, Blount's rule is a good one. "Don't throw away the cane."

Reparative osteogenesis is basically a problem in protein metabolism and is only



a b

FIG. 2. Osteoporotic bone produces osteoporotic callus.

incidently related to the secondary deposition of bone salts. This observation is related to the question of hormone therapy in fractures of the aged. There is still much to be learned about the effect of androgens and estrogens on bone repair. No convincing evidence has been found of any increased trabecular density even when they were used in cases of senile osteoporosis. However, since the purpose of the androgens in this circumstance is said to be that of saving or retarding the resorption phase of the protein matrix one cannot use x-ray film densities as an index of their function. Although there was often a clinically apparent sense of well-being enjoyed by some patients during the period of hormone therapy, no specific effect on the rate or quality of bone repair was observed.

A final observation on the treatment of bed-care patients applies to the constant demand of early "out of bed." The benefit of this is of course incontrovertible when its purpose is gained. However, too often the order is obeyed to the patient's actual detriment. To be out of bed sitting gently in a comfortable chair, free to move the arms and legs, to shift position, to reach for nearby objects is the virtue of this practice. But to be lifted out of the freedom of a roomy and adjustable hospital bed and then to be immobilized in a sitting position by the cautious blanketing of a solicitous attendant who fears more the pneumonia of a draught than the hypostasis of bed is indeed a gross disservice. Getting the patient out of bed must mean greater freedom of action; it must not lead to the straight jacket of tender and loving care.

Actually the rules governing the general management of fractures of the elderly are simple enough. There are no special techniques. There is merely a recognition of the organic limitations of aging structures, the lessened resiliency of the tissues, and the choice of tools and forces to meet these circumstances. Excessive external or metallic fixation or undue zeal in muscular or articular rehabilitation may be utterly futile in an elderly person whose physical activities have been progressively restrained for some years before the fracture occurred. The simplest procedures compatible with a functional recovery adequate for his physical abilities will serve the aged patient far better than a tour de force directed to an unobtainable objective.

REFERENCES

1. Bick, E. M. Healing of fractures. Am. J. Surg., 1950, 80: 843.
2. Blount, W. P. President's Address: American Academy Orthopaedic Surgery. J. Bone Surg., 1956, 38A: 695.

INTRACYSTIC CARCINOMA OF THE BREAST

FRANK G. GATCHELL, M.D., MALCOLM B. DOCKERTY, M.D., and

O. THERON CLAGETT, M.D., F.A.C.S., Rochester, Minnesota

THE INITIATION of this study came as the result of encountering, in the laboratory, a carcinoma of the breast which had apparently arisen from the wall of a "blue-domed" cyst. A review of the English literature failed to reveal any significant series of such cases. It was decided, therefore, to undertake a study of experience with intracystic carcinoma of the breast at the Mayo Clinic.

HISTORICAL BACKGROUND

Little correlated knowledge of cystic disease of the breast was evident in the literature until 1825 when Sir Astley Cooper (7) made his detailed study.

Subsequently, several small series of cases and other reports of single cases of mammary cystadenocarcinomas have been presented in the literature. From a study of these cases the following four facts emerge: (1) many of the growths are papillary; (2) occasional cancers of the apocrine sweat gland occur in this category; (3) the clinical picture often suggests benign pathologic conditions of the breast, and (4) the prognosis, in general, is good.

MATERIAL AND METHODS

For purposes of securing enough material to make the study of statistical significance it was decided to cover a 35 year period (1920 to 1954), during which time more than 9,000 breasts had been removed at the clinic because of primary malignant disease. Pathologic reports were scrutinized for gross descriptions which included such terms as "cancer cyst," "carcinoma arising in a cyst," "intracystic papillary carcinoma," "papillary cystadenocarcinoma," or some similar designation, and 88 potential cases were selected for inclusion in the series. However, 40 were discarded for the following reasons: (1) in 31 instances the tumors were considered benign on histologic review; (2) in 4 no tumor was grossly demonstrable; (3) 2 specimens were unsuitable for adequate study; (4) in 1 case the cancer was associated with "chronic cystic mastitis," but was not intracystic; (5) 1 specimen was an example of central necrosis in a solid carcinoma, and (6) 1 tumor was located in the wall of a large abscess. The 48 remaining cases formed the basis for our study. All specimens used had been preserved in 10 per cent formalin and they were assembled for analysis according to size and position of the cyst, unilocular versus multilocular characteristics, whether papillary or solid, and so forth. New sections were cut and stained routinely with hematoxylin and eosin. These were added to the original sections so that some 350 histologic sections were available for study.

Pertinent clinical data were recorded on file cards for easy tabulation. All patients except 2 had been re-examined at the clinic or had replied to regularly sent letters of inquiry. A specific attempt was not made to study either the type or the incidence of associated benign lesions in the affected breast.

CLINICAL FINDINGS

The occurrence of intracystic carcinoma in 48 of 9,000 cases of breast cancer at the clinic from 1920 to 1954 produces an incidence of 0.5 per cent for this type of carci-

From the Sections of Surgical Pathology and Surgery, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Gatchell to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

TABLE I.—INTRACYSTIC CARCINOMA OF THE BREAST: 48 CASES, 53 TUMORS

	*Grade of the tumor**			
	1	*2*	*3*	*4*
Specimen†	22	25	5	6
Per cent‡	37.9	43.1	8.6	10.3

*Broders' classification.
†Several tumors had specimens of more than one cytologic grade making a total of 58 that were graded.
‡Percentages are calculated on the basis of 58.

noma. All patients were women. The average age was 57.3 years, with a range from 21 to 83 years inclusive. Forty-six per cent of the tumors affected women between the ages of 41 and 60 years. Eighty-one per cent of the patients were, or had been, married; 69 per cent had borne children and 10 per cent of these had had 1 or more miscarriages. Of the 48 patients, 15 per cent had had some form of menstrual abnormality, and 60 per cent were menopausal at the time their tumor was discovered.

Fifty-three intracystic tumors were encountered in 48 patients. Twenty-nine (54.7 per cent) of the tumors occurred in the left breast and 24 (45.3 per cent) in the right. Four patients had 2 tumors in the same breast. In 1 of these 4 patients, 2 separate tumors were present in different locules of a cyst; in the other 3 the second tumor was not intracystic but was one of the commoner types of breast cancer. One other patient had a synchronous scirrhous adenocarcinoma, grade 4, in the opposite breast. Four patients had bilateral cancers which were metachronous. In 1 of these patients, the tumor in the opposite breast developed before the intracystic carcinoma, and in 3 patients the tumors occurred after removal of the intracystic growth. In none of the latter 3 patients was the second tumor of the same grade or histologic type as the first. It must be assumed, therefore, that the second tumor was not an ipsilateral metastatic lesion from the first tumor.

TABLE II.—ARCHITECTURAL PATTERNS (HISTOLOGIC) IN INTRACYSTIC CARCINOMA OF THE BREAST

Histologic patterns	*No. of specimens**	*Percentage†*
Papillary	33	56.9
Scirrhous	5	8.6
Comedo	10	17.2
Mucinous (colloid)	1	1.7
Sweat gland	3	5.2
Adenoacanthoma	2	3.4
Carcinosarcoma	1	1.7
Lobular carcinoma in situ	3	5.2

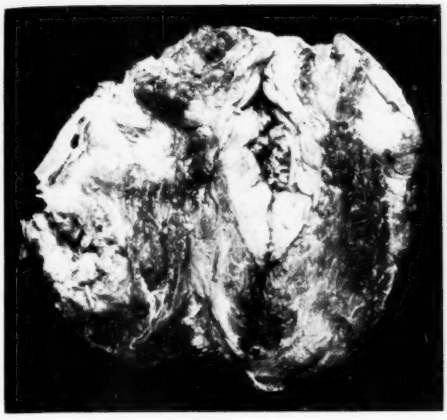
*Several tumors exhibited more than one architectural pattern; a total of 58 were observed.
†Percentages are calculated on the basis of 58.

The tumors were located most frequently in the central or subareolar portion of the breast, 36 per cent being found in this location. Approximately 18 per cent of the tumors were located in each of the upper outer, the upper inner, and the lower inner quadrants. Ten per cent were present in the lower outer quadrant of the breast.

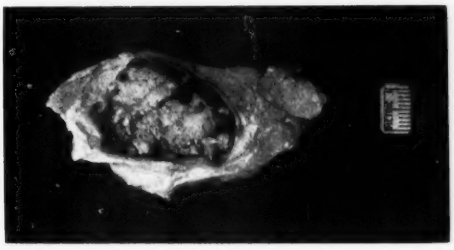
Ninety per cent of the patients came for examination because of the discovery of a mass in the breast. Sixteen patients (33 per cent) first noted a discharge from the nipple, and 14 (29 per cent) noted a discharge and a mass simultaneously. In 11 (23 per cent) the discharge was bloody. Twelve (25 per cent) noted pain as the first symptom, usually described as an "uncomfortable feeling" or "sticking sensation." Forty-four patients (92 per cent) presented a single mass on examination; 6 (13 per cent) had more than 1 palpable mass. This is not to imply that the division into single and multiple nodules was as simple as this enumeration might make it seem. In some of the patients associated regions of "cystic mastitis" were palpable as multiple "shotty" nodules. In the instances already noted the cysts were rather distinctly separable from the surrounding tissue. The average duration of the palpable mass was 35.3 months with a range of 3 days to 59 years. In those patients with nipple discharge as a primary complaint, the average duration of the discharge was 39 months, with a range of 1 week to 12 years.

PATHOLOGIC FINDINGS

Gross. In 42 of 48 cases a single cyst was noted, 4 of which were multiloculated. In the remaining 6 cases more than 1 intracystic tumor was present. In 23 cases (48 per cent) more than 1 mass was attached to



a



b

FIG. 1. a, Papillary cystadenocarcinoma, grade 2, in the wall of a 5 centimeter mammary cyst. b, Close-up of lesion.

the wall of the cyst. In 17 of these, all of the intracystic masses were grossly shaggy and papillary; in 6 the nodules were solid. In 25 cases (52 per cent) only 1 intracystic mass was present. Of these, 17 were grossly papillary and 8 were solid.

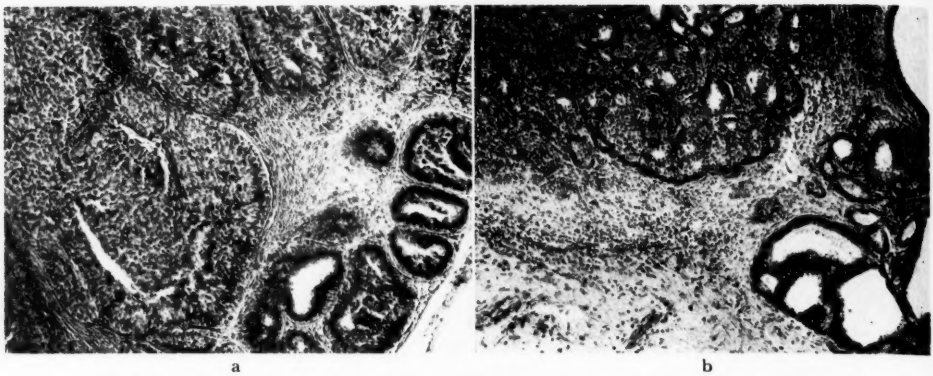
The cysts containing the tumors ranged in size from 1.5 to 10 centimeters in diameter, but the majority were from 2.5 to 4 centimeters in diameter. In their noncarcinomatous portions most of the cysts exhibited thin walls, usually not more than 1 millimeter in thickness.

The solid intracystic nodules appeared as smooth, round to ovoid masses attached to the wall of the cyst. The papillary lesions presented as delicate, frondlike, friable projections springing from broad bases, and in no instance was an isolated stalk demonstrable. Figures 1 and 2 are rather typical examples of the gross features of most of the low grade papillary carcinomas encountered in this series.

Microscopic. Histologically, the tumors in this series exhibited examples of all 4 cytologic grades (Broders' classification) as well as almost all of the well known architectural patterns, namely, papillary, scirrhous, comedo, mucinous, sweat gland type, adenoacanthoma, carcinosarcoma, and lobular carcinoma in situ. The number of cases in each category can be seen in Tables I and II. Each of the various architectural types was in every way typical of that specific type except for its intracystic location.

Several of the tumors deserve special mention because of their unusual features. Within one cyst was a mixed papillary adenocarcinoma, grades 1 and 2; a metastatic lesion in an axillary lymph node maintained the same mixture of grades as that of the primary lesion (Fig. 3a and b). Another tumor classified as a "mucous adenocarcinoma" exhibited features of both a high grade and a low grade lesion (Broders) in that there were "signet-ring" cells (intracellular mucus, indicative of high grade) and pools of extracellular mucus (indicating a low grade lesion) (Fig. 4). In

FIG. 2. Papillary cystadenocarcinoma, grade 1, in the wall of a 4 centimeter mammary cyst.



a b

FIG. 3. a, Mammary adenocarcinoma showing a mixture of cells of both grades 1 and 2 in one microscopic field. Hematoxylin and eosin, ×77. b, Same tumor as shown in "a" metastasized to a single axillary lymph node, each element maintaining its individual grade. Hematoxylin and eosin, ×77.

1 case a carcinosarcoma was present. This tumor was a papillary adenocarcinoma, grade 3, with regions of fibrosarcoma that contained areas of osteogenesis (Fig. 5a and b). Two of the tumors were adenoacanthomas. Both were grossly papillary lesions, cytologically grade 2, and contained nearly solid sheets of squamous cells. Three tumors presented cytologic evidence suggesting origin in apocrine sweat glands (Fig. 6). The histologic sections showed them to be composed of large, pale, granular, eosinophilic cells very closely resembling those seen in Schimmelbusch's disease. We do not propose to designate these as unequivocal examples of this type of tumor, but the histologic appearance was strongly suggestive of an apocrine origin of the component cells. In 3 tumors, areas of lobular carcinoma in situ, as described by Foote and Stewart (2), were discovered incidentally during routine microscopic examination of the sections (Fig. 7).

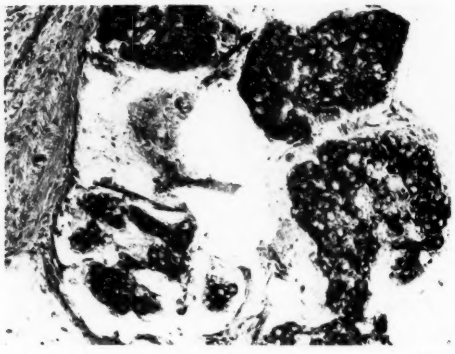


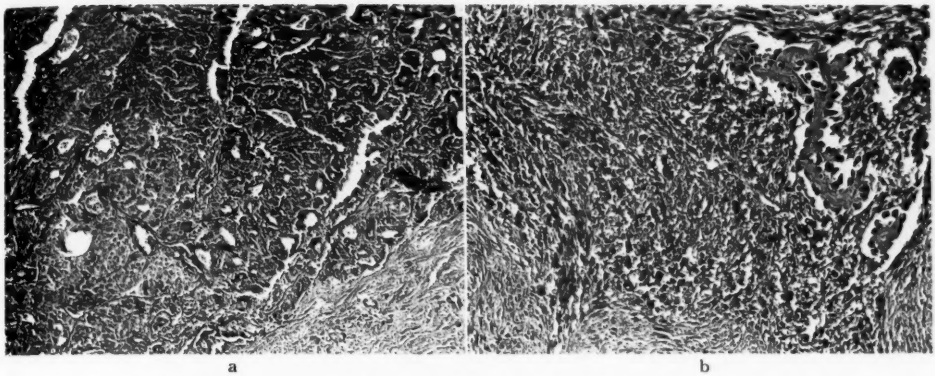
FIG. 4. Mucinous cystadenocarcinoma showing pools of extracellular mucus in certain areas and "signet-ring" cells in others. Hematoxylin and eosin, ×74.

Fifteen tumors showed definite histologic evidence of invasion of the cyst wall, 4 showed invasion of microscopic veins and 7 showed invasion of small lymphatics. Four presented definite areas of ductal hyperplasia in the surrounding mammary tissue.

Axillary nodes were available for study in 35 cases; in 3 tumors metastasis to these structures was exhibited. One tumor was the mixed papillary tumor of grades 1 and 2 previously mentioned (Fig. 3a and b). Another was a mucinous adenocarcinoma, grade 3 (Fig. 4), and the third was a mixed comedo and scirrhous adenocarcinoma, grade 4.

TREATMENT AND SURVIVAL OF PATIENTS

A brief recounting of the types of treatment employed might be of interest in passing. In 29 patients radical mastectomy alone was done, and in 6 others this opera-



a b

FIG. 5. a, Mammary cyst containing a mixture of carcinomatous and sarcomatous elements (carcinosarcoma). b, Section of fibrosarcoma with osteogenesis in same tumor as shown in "a".

tion was supplemented by postoperative irradiation therapy. In 8 cases the treatment was simple mastectomy; in 4 others simple mastectomy was supplemented by irradiation postoperatively. In the remaining case, local excision of the mass was the only treatment.

Of the 48 patients in the series, 36 were eligible for 5 year follow-up studies. Of these, 30 were living and well at the time of the last available information, a 5 year survival rate in this series of 83.3 per cent.

COMMENT

Since the papillary tumors were the largest single group in this series, there are several additional points worthy of note. We wish to re-emphasize the fact that 31 of the original 88 cases were discarded because on critical review the tumors were considered to be benign. Some of these were actually borderline and might have been included. This study does show, however, that there are examples of low grade papillary carcinomas which are definitely malignant and capable of metastasizing. It is not within the scope of this article to debate the point of whether or not malignant transformation of a benign papilloma occurs, or whether such a lesion is malignant from its inception. That such a change can occur, however, seems to be a reasonable point of view, for

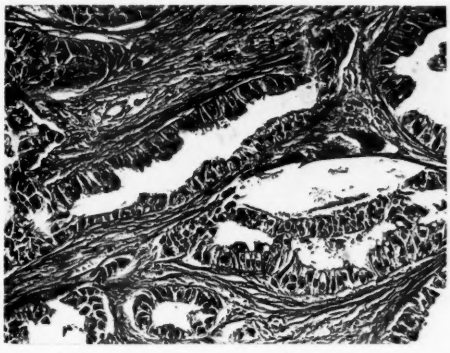


FIG. 6. Cystadenocarcinoma, grade 2, the component cells of which resemble epithelial cells of apocrine sweat gland. Hematoxylin and eosin, ×74.

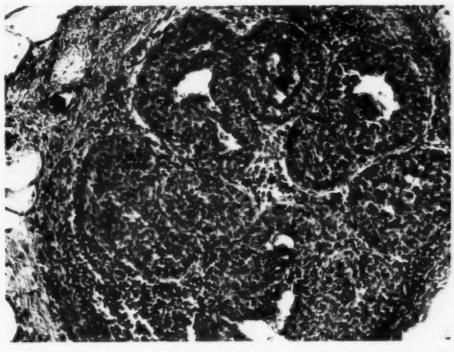


FIG. 7. Lobular carcinoma in situ, grade 2, in a cystadenocarcinoma which elsewhere showed mainly papillary adenocarcinoma, grade 2. Hematoxylin and eosin, ×110.

in at least 4 of these cases histologic evidence of such change was striking, and in 2 others it seemed very probable.

Whether or not a cyst in the breast arises from a terminal ductule or from an alveolus or from both, unfortunately, has not been determined. It seems reasonable to believe that such cysts can arise from either type of structure, but we tend to favor the view that in the large majority of cases the cysts are of ductal origin. The finding in this series of a wide variety of architectural patterns, that is, those which are commonly seen in cancers of the breast which are not intracystic, tends to support this view, since most authorities believe that the usual cancer of the breast is ductal in origin. One of the most striking things in the series is this variety of histologic lesions which apparently can arise from the wall of a cyst. This has been pointed out by Foote and Stewart (4, 6) and is confirmed by this study.

There were several tumors in the series in which more than 1 cytologic grade (Broders) or more than 1 architectural pattern was present. These findings seem somewhat unusual, and we do not know of any good explanation for their occurrence.

The role of apocrine sweat gland epithelium in breast cancer is interesting. Early writers were of the opinion that this cell type gave rise to 20 or 25 per cent of all breast cancers. Today, however, the consensus is that although such tumors do exist, they are certainly much rarer than they were originally considered. Lee and associates, in 1933, reported a series of 81 such cases, and Foote and Stewart (3) found 3 cases in a series of 300 breast cancers. As previously noted, our series contains 3 tumors in which the component cells strongly resemble those derived from apocrine epithelium.

SUMMARY AND CONCLUSIONS

Findings in a series of 48 cases of intracystic cancers of the female breast have been presented. This series was gleaned from 9,000 cases of breast cancer of all types encountered at the Mayo Clinic during the 35 year period 1920 to 1954. As far as we were able to determine from a careful study of both the gross and microscopic features of these tumors, their origin was from, or near, the lining of the cysts which contained them.

Included in the series were examples of all 4 cytologic grades of malignancy according to Broders' classification, and all major architectural patterns; this led us to agree with Foote and Stewart (4) that "these tumors are more of a gross than a microscopic entity."

As might be expected, the prognosis for tumors of this type is considerably better than in the usual type of breast cancer. The over-all 5 year survival rate in this series is 83.3 per cent.

These tumors are rare, the incidence at this particular institution being approximately 0.5 per cent. That they do occur, however, must be kept in mind when biopsy of a specimen from the breast for supposedly benign cystic disease is performed.

REFERENCES

1. Broders, A. C. Squamous-cell epithelioma of the lip; 537 cases. J. Am. M. Ass., 1920, 74: 656-664.
2. Foote, F. W., Jr., and Stewart, F. W. Lobular carcinoma in situ. Am. J. Path., 1941, 17: 491-495.
3. Idem. Comparative studies of cancerous vs. noncancerous breasts. Ann. Surg., 1945, 121: 6-53, 197-221.
4. Idem. Histologic classification of carcinoma of breast. Surgery, 1946, 19: 74-99.
5. Lee, B. J., Pack, G. T., and Scharnagel, Isabel. Sweat gland cancer of the breast. Surg. Gyn. Obst., 1933, 56: 975-996.
6. Stewart, F. W. Tumors of the breast. In: Armed Forces Institute of Pathology. Atlas of Tumor Pathology, Section IX, Fascicle 34. Washington, D. C.: National Research Council, 1950.
7. Tyrrell, Frederick, editor. Lecture XX. Diseases of the breast. In: The Lectures of Sir Astley P. Cooper on the Principles and Practice of Surgery. Vol. II., pp. 125-145. Boston: Lilly and Wait, 1831.

EDITORIALS

THE CANCER CONTROVERSY

J. ENGLEBERT DUNPHY, M.D., F.A.C.S., Boston, Massachusetts

IN THE LAST TWO DECADES the satisfaction and complacency of surgeons concerning the effectiveness of the surgical treatment of cancer have been shaken. Prior to that time there was a general conviction that if the diagnosis could be made early enough, surgical excision would assure a cure. The full realization that this is not the case (actually a fact clearly evident to students of cancer for many years) has led to a controversy among surgeons which is assuming more prominence than it merits. Much of the disagreement is a matter of semantics.

Broadly speaking, one group of surgeons advocates a reappraisal of the entire cancer problem, emphasizing the importance of the biologic nature of cancer as a factor in its treatment rather than the time or extent of surgical therapy employed. The other group would hew to the line of surgical orthodoxy, re-emphasizing the importance of the very earliest possible diagnosis and the most radical excision. In actual practice, however, one finds that the management of the individual case is remarkably similar no matter which group of surgeons is involved.

Unfortunately, however, the argument has reached the stage where emotion and a certain degree of acrimony are playing a greater role in the discussions and in publications than an honest and scientific evaluation of the facts. The facts are these: First, it is evident that despite 50 years of surgical progress cancer is incurable in over 50 per cent of the cases. In certain cancers the absolute cure rate is not greater than 10 per cent. This can hardly be regarded as grounds for complacency or satisfaction. Secondly, the extended radical operations for cancer, although thoroughly justified in carefully controlled studies, have not as yet been shown to effect survival rate to any dramatic degree. Indeed, what evidence is available, such as the studies of Naunton Morgan with reference to high ligation of the inferior mesenteric artery in the treatment of cancer of the rectum and of Dahl-Iversen with respect to mediastinal node dissection for cancer of the breast, indicates that the extended operation as a routine is not going to solve the problem of cancer therapy. For this reason those who undertake extended operations for cancer should not promote their general and routine adoption before more evidence is available. The morbidity and mortality occasioned by needless, ill-advised or improperly executed, supraradical operations undertaken by the average surgeon because he thought he was obligated to do them, are hard to assess, but certainly not inconsiderable.

This is not to say that there is no place for extended operations. The surgeon who hesitates to do a hindquarter amputation for sarcoma of the hip or an en bloc excision of the tongue, jaw, and neck for an operable cancer of the tongue is not providing the best possible therapy and should not attempt

From the Department of Surgery, Harvard Medical School; The Fifth Surgical Service and Sears Surgical Laboratory, Boston City Hospital.

to treat such lesions by limited procedures. Similarly, at fault is the surgeon who will not do a radical gastrectomy, splenectomy, colectomy, and partial pancreatectomy for a locally invasive but resectable carcinoma of the stomach. This is a far cry, however, from saying that these procedures should be done for every tumor in such locations. Indeed the great significance of the biologic approach to cancer surgery is the emphasis which it places upon the fact that certain cancers require big operations and that in others the same operation is an unjustifiable sacrifice of the patient. Moreover there are some cancers which may be best treated by less radical or particularly designed operations. This is not therapeutic nihilism as some orthodox surgeons have cried. It is, in fact, exactly what most experienced cancer surgeons in this country are doing. An example? Simple mastectomy for an ulcerating scirrhous carcinoma of the breast of 5 years' duration without evident axillary involvement in an 80 year old woman!

It must also be emphasized that in our present state of ignorance there is no justification for abandoning the standard procedures in cancer surgery. Although it is possible that limited excisions in all instances regardless of age will prove to be as efficacious as the more radical operations for certain cancers, the data at hand do not permit such conclusions now. Here again carefully controlled study rather than widespread advocation is indicated.

The most hopeful trend in cancer surgery today is the emphasis which is being placed upon more skillful surgery. The hazards of local implantation, the great importance of experience in recognition and interpretation of gross pathology during the operative procedure, the need for supplementary irradiation or hormonal therapy in certain instances, and the adoption of special measures, such as local chemotherapy or preoperative irradiation to prevent dissemination are aspects of cancer surgery which require that it be performed by the most experienced and specially trained surgeons. It is reprehensible for the occasional operator who would not undertake a radical mastectomy to perform a simple mastectomy and then refer the patient to a larger center for irradiation. A properly performed simple mastectomy, although perhaps easier on the patient, requires as much skill and care on the part of the surgeon as a radical mastectomy. Its proper place in conjunction with x-ray in the treatment of cancer of the breast can be established only in the hands of the most experienced surgeons.

Finally, although it is evident that time alone is not the essence of successful cancer surgery, there is no reason to de-emphasize the desirability and importance of early diagnosis. Any disease should be recognized as early as possible and cancer is no exception. This should therefore be encouraged by a sensible program of public education.

Meanwhile what is needed is more information, knowledge, and understanding of the nature of cancer. More facts and less emotion are in order.

ABDOMINAL INJURIES DUE TO BLUNT FORCE

EDWIN M. MILLER, M.D., F.A.C.S., Chicago, Illinois

EVEN BEFORE THE ERA of the "horseless carriage" reports of abdominal injuries due to blunt violence occupied a prominent place in the surgical literature because of their extremely high mortality. But with the advent of the automobile and the ever increasing number of serious accidents on the highway, rarely involving only one part of the body, these abdominal injuries have assumed a position of even greater importance, because they are too frequently overshadowed by the more evident concomitant injuries of the head, chest, and the extremities, and therefore may be overlooked entirely or their presence discovered so late that surgical intervention is of no avail.

Blunt violence to the abdomen frequently results in injury to the liver and spleen. Though partially protected by the lower part of the chest a severe blow or crushing injury in this area may not only fracture several ribs but easily produce a rupture of either one or both of these solid organs, with bleeding into the free abdominal cavity. If the loss of blood is considerable the clinical signs of hemorrhagic shock soon appear, the abdominal muscles become tense, bowel sounds are diminished, dullness may be elicited in one or both flanks, and the need for emergency operative intervention is quite apparent.

The stomach, overlying the rigid vertebral column in its distal half, is especially vulnerable to a direct blunt force when it is distended with fluid. The resulting tear, if on the anterior wall, permits the stomach contents to spill directly into the abdominal cavity, where it immediately causes a chemical peritonitis with easily detectable generalized board-like muscle rigidity, whereas if the posterior aspect of the stomach is involved the escaping fluid enters the lesser sac, where it is less apt to produce immediately recognizable clinical evidence of its presence, and therefore may result in a dangerous delay in surgical intervention. Associated tears of the vessels of the torn stomach wall may of course result in rapid loss of a large amount of blood.

The loops of small intestine, especially when empty, are more or less mobile and are free to move quickly out of the way of injury and may at times miraculously escape any damage, but the mesentery of the small bowel being fixed at its base is frequently torn in several places producing multiple areas of active bleeding.

The colon because of its fixed position, except in its transverse portion, may be easily ruptured when distended. The gas and fecal content may escape directly into the free abdominal cavity, where they rapidly set up a general peritonitis resulting in profound shock; or the tear may be entirely retroperitoneal, allowing the bowel contents to spread upward or downward along the lateral gutter into tissues which offer little resistance to infection. In the latter instance, if the perforation be small, clinical evidence of this extremely serious injury may make its appearance very slowly and thus tend to delay surgery too long.

The duodenum has a vulnerability peculiarly its own, even though it is less frequently involved by blunt trauma than are the small intestines and colon. The duodenum is anatomically more or less fixed in position, lies directly over the hard unyielding vertebral column, and when distended with fluid is potentially a closed loop, being constricted proximally by the pyloric sphincter and narrowed distally by the overlying superior mesenteric vessels. It is therefore, like a toy balloon, easily ruptured by even a mild direct blow if the force is applied so suddenly that the involuntary

defense of the contracted abdominal muscles has not had time to exert itself. The resulting tear in the duodenal wall though sometimes occurring anteriorly in the second portion, too frequently takes place on the posterior side where it is entirely retroperitoneal. This permits bile and air and digestive juices to escape into a very vulnerable space where, if the rent be a small one, a cellulitis or phlegmon can develop before its presence is demonstrable clinically.

It is quite evident, therefore, that the doctor who is called upon to care for the victim of these potentially serious injuries is faced with a grave responsibility, and often with a complex clinical problem which may tax his judgment to the utmost. He will be a wise man if he always realizes the necessity for immediate action even though the time be in the middle of the night, for a few precious hours can make the difference between a life and a death. If the injury has very clearly been limited to the abdomen the problem is somewhat simplified, but if it has been due to an automobile accident the very evident injuries to the head, chest, and extremities may immediately overshadow everything else and allow a potentially serious but not immediately recognizable abdominal lesion to remain undiscovered too long. The surgeon must, of course, deal with the most urgent things first, i.e., secure an adequate open airway, stop external bleeding, cover open wounds, apply necessary splints, insert a Levin tube in the stomach, pass a catheter into the bladder, and bend every effort to combat shock with blood transfusions; but during the time when these all important urgent procedures are being carried out he must never fail to evaluate the presence of any symptom referable to the abdomen, no matter how slight, or any physical finding even suggestive of abdominal trauma, remembering always that a relatively minor injury may rupture a bowel, and a serious injury may at times leave no visible marks of violence. Certain x-ray films will be of great value, particularly when the head, chest, or extremities are involved, and occasionally films of the abdomen will reveal something of real importance, i.e., free air under the diaphragm or obliteration of psoas or kidney shadow, but valuable time can be lost by too much debate about negative evidence, time which might be used to better advantage by getting the patient to the operating room.

Having decided that the abdomen must be opened, what is the logical procedure? Inasmuch as a wide exposure is usually necessary one would do well to consider using a long right paramedian or a transverse incision just above the umbilicus, for both of these permit free access to both upper and lower abdomen and also to both lateral gutters. The character of the gas or free fluid in the abdomen, if any be present, will of course give one an immediate clew to the source of the trouble. Massive bleeding is most apt to be from a torn liver, spleen, gastric or mesenteric vessels, and must be dealt with first. Odorless gas or colorless fluid will suggest a tear in the stomach, bile-stained frothy fluid a rent in the duodenum or upper small bowel, brownish fluid a probable rupture of lower ileum, fluid with a fecal odor mixed with solid material a lesion of the large intestine. The exploration must be thorough and systematic, even though an obvious lesion is immediately found. Careful inspection of the upper abdomen should reveal a tear if it is in the anterior wall of stomach or duodenum, but one must not forget to open the gastrocolic ligament to determine whether there is a contamination of the lesser peritoneal sac. Perforations of the small bowel are quite readily found, as are tears of its mesentery, especially if one begins the search at the ligament of Treitz and examines every loop until the cecum is reached. Closures of the small bowel are best made transversely, and end-to-end anastomosis lends itself very well if resection be necessary. Lesions of the colon may give one considerable trouble unless adequate exposure has been accomplished by mobilization of both hepatic and splenic flexures and incisions into both

lateral gutters. In this way only can one be certain that a retroperitoneal leak has not occurred. If, fortunately, the operation has been done early (within the first few hours), perforations of the colon can be safely closed and lateral drainage established without the necessity for a colostomy.

Finally, we come to a consideration of a possible tear in the retroperitoneal part of the duodenum, reserving it intentionally until the last because of its extreme importance. At first glance in the right upper quadrant nothing abnormal may have been noticed (especially if only a few hours since injury) and, having already taken care of obvious bleeding or perforation elsewhere, the surgeon might feel justified in omitting further exploration. Let us warn against any feeling of security on this point until he be absolutely certain. We would urge him to look again, with a good light, at the peritoneum at the base of the right transverse mesocolon and just lateral to the second part of the duodenum. Is it at all discolored yellow or green? Is it hemorrhagic or edematous? Is there crepitation? We would advise him to divide the peritoneum just as he would do in mobilizing the duodenum when searching for a stone at the ampulla of Vater or pancreatic portion of the common duct, and, unless it already has been done, mobilize the hepatic flexure of the colon medially so that he will have a good view of the entire retroperitoneal area. If he can detect no gas or greenish stain, and finds no blood in this area he can feel assured that there is no tear in the duodenum. On the other hand, when any of these abnormal findings are present he must continue the search until the tear is found. If the operation has been done early the margins of the opening in the duodenum may be safely closed, but if it has been delayed too long there will be in this region a collection of foul-smelling gas and fluid, and the edges of the perforated wall will be friable and edematous. Under these conditions in spite of his best efforts at closure, with drainage and the use of antibiotics, it may be difficult if not impossible to avoid a fatal outcome.

The surgeon may occasionally close an abdomen after thorough search for suspected pathologic conditions without finding anything abnormal, and he may feel much chagrined because he has subjected his patient, already suffering from concomitant injuries elsewhere, to an unnecessary operation; but, on the other hand, he will have made certain that a hidden serious lesion has not been overlooked, and he will have a patient recovered rather than a death due to his neglect.

THE SURGEON AT WORK

OPERATIVE ASPECTS OF RICHTER'S HERNIA

FAWZI PUALWAN, M.D., Medical Corps, Army of the United States

RICHTER'S HERNIA is an unusual type of hernia in which only part of the circumference of the bowel wall is incarcerated in the sac. The early signs of strangulation encountered in this type of hernia are quite mild and unimpressive resulting in a delay in recognition which in turn is responsible for the high associated mortality rate.

The stimulus for the preparation of this article resulted from personal experience with 6 cases of Richter's hernia seen during 1956 at the Strong Memorial Hospital. Five of these were in femoral hernias and 1 in an umbilical hernia. An extensive review of the literature fails to show a uniform surgical approach for the treatment of this type of hernia.

In 1598 Fabricus Hildanus[1] gave the case history of a 63 year old woman with a 17 year history of a hernia in the groin which suddenly became strangulated resulting in gangrene and abscess formation, and subsequently it drained externally with a persistent fecal fistula for about 2 months. Since the fistula closed spontaneously, Hildanus concluded that only part of the circumference of the intestine was constricted. This probably represents the first description of what is now generally recognized as a Richter's hernia.

Alexis Littré (1658–1726) described the first case of herniation of the congenital Meckel's diverticulum although he was not aware of this congenital anomaly, and it was not until 1815 when Meckel accurately described the diverticulum which now bears his name that the true nature of Littré's hernia came to light. The term Littré's hernia should be reserved only for those hernias containing a Meckel's diverticulum.

From the Department of Surgery of the University of Rochester School of Medicine and Dentistry, Rochester, New York.

[1] Cited by Treves.

In 1785, August Richter (1742–1812) gave the first complete description of hernias in which only part of the bowel wall was strangulated thus differentiating this condition from that described by Littré.

In 1931, Frankau reviewed 1,487 cases of strangulated hernia which included 654 inguinal, 680 femoral, and 153 umbilical hernias. In the 654 cases of inguinal hernia he found 4 cases of Littré's hernia (an incidence of 0.6 per cent) and 15 cases of Richter's hernia (an incidence of 2.2 per cent). In the 680 cases of femoral hernia, there was 1 case of Littré's hernia (an incidence of 0.14 per cent) and 77 cases of Richter's hernia (an incidence of 11.3 per cent). There were 2 cases of Richter's hernia in the 153 cases of umbilical hernia, an incidence of 1.3 per cent. Further analysis from this excellent statistical review shows that 83 per cent of the Richter's hernias were found in femoral hernias and the over-all mortality for the 94 cases reported was 20.2 per cent. These figures are similar to those reported by Bissell, Cattell, and Gillespie, and although the mortality rate is still quite high it represents a marked improvement over the 62.2 per cent reported by Treves.

CASE REPORTS

The 6 case reports that follow illustrate the diagnostic and therapeutic problems presented by this type of hernia.

CASE 1. S. P., a 72 year old female, was admitted on January 19, 1956 with a 2 year history of a reducible mass in the right femoral region which had become irreducible 2 days prior to admission and was associated with right, lower quadrant crampy pain and repeated emesis.

Physical examination revealed: temperature 37.3 degrees C., pulse 80, respiration 20, and blood pres-

sure 132/80. She was very thin and dehydrated. The abdomen was distended, minimally tender with visible hyperactive peristalsis and occasional rushes. A small irreducible mass was felt just inferior to the inguinal ligament. Laboratory studies were normal except for a white blood count of 16,400. The preoperative diagnosis was small bowel obstruction and femoral hernia on the right side. A right inguino-abdominal incision was made under spinal anesthesia and a Richter's femoral hernia was found on the right involving a portion of the antimesenteric border of the ileum. The hernia was reduced with gentle traction and no resection was necessary. The hernial sac was everted and excised and the hernial defect repaired. The preoperative course was benign, and the patient was discharged on the twelfth postoperative day.

CASE 2. I. H., a 77 year old woman, while in the hospital for care of a radiation ulcer of the right upper arm on January 26, 1956 suddenly developed a tender 10 centimeter mass just inferior to the right inguinal ligament without previous history or physical findings of a hernia. Except for a slight hypochromic anemia, the laboratory findings were all within normal limits. Under general anesthesia, using a right inguino-abdominal incision, a Richter's femoral hernia was found involving a portion of the antimesenteric side of the cecum. A small incision in the edge of the lacunar ligament was necessary to free the incarcerated loop. The cyanotic appearance of the incarcerated segment promptly disappeared and resection was unnecessary. The peritoneum was closed and a femoral herniorrhaphy carried out. The postoperative course was uncomplicated.

CASE 3. M. T., a 76 year old woman, was admitted to the emergency division on March 2, 1956 in a disoriented state with the referring diagnosis of intestinal obstruction and a 2 week history of lower abdominal pain and recurrent vomiting.

Physical examination revealed: temperature 38.2 degrees C., pulse 100 irregular, and respiration 40. She was disoriented and cyanotic and the blood pressure was unobtainable. The abdomen was distended and there was no apparent tenderness or peristalsis. A 2.5 centimeter, round, nontender mass presented just inferior to the right inguinal ligament. During the examination she vomited 600 cubic centimeters of fecal-like fluid. Laboratory studies showed: hemoglobin 22.5, white blood count 11,500, urine negative, serum sodium 123 milliequivalents per liter, potassium 5 milliequivalents per liter, chlorine 74 milliequivalents per liter, carbon dioxide 30 milliequivalents per liter, and nonprotein nitrogen 180 milligrams per cent. The preoperative diagnosis was Richter's femoral hernia on the right side with strangulation and intestinal obstruction. Initial treatment consisted of intravenous fluids, nasal oxygen, gastric aspiration with return of 4 liters of foul brown gastric content, digitalization, and transfusion with 500 cubic centimeters of blood. The blood pressure gradually rose to 108/60 but the urinary output remained minimal until 15 hours after admission. Three hours later she had improved sufficiently to permit surgical intervention. A right inguino-abdominal incision was made under cyclopropane anesthesia revealing a Richter's femoral hernia containing a knuckle of terminal ileum. The appendix which was gangrenous was tightly drawn into the hernia alongside the ileum. A perforation of the ileum was present at the neck of the sac with surrounding peritonitis. The terminal ileum, cecum, and ascending colon were infarcted with thrombosis of their blood supply. The edge of the lacunar ligament was divided to release the hernial contents. The terminal ileum, cecum, and ascending colon were resected and an end-to-side ileotransverse colostomy was performed. The open end of the transverse colon was exteriorized as a colostomy through the lateral aspect of the incision. A rapid repair of the femoral canal was carried out.

Postoperatively she showed rapid improvement. She became increasingly more responsive, and a good urinary output was maintained. On the third postoperative day she evacuated spontaneously via the colostomy and rectum and her diet was gradually increased to include soft foods. On the eighth postoperative day she suddenly expired without warning. Autopsy was refused. The probable cause of death was pulmonary embolism or coronary occlusion.

CASE 4. L. S., a 79 year old woman, was admitted on July 17, 1956 with a 3 day history of crampy abdominal pain and 2 days of vomiting. Physical examination revealed a dehydrated patient with moderate abdominal distention and hypoactive peristalsis. A mass was felt in the left femoral area. Gastric aspiration produced 1,200 cubic centimeters of fecal fluid. She was hydrated and urinary output gradually increased. The preoperative diagnosis was incarcerated femoral hernia of the left side with partial small bowel obstruction. Twenty hours after admission she was taken to the operating room and under spinal anesthesia a left inguino-abdominal incision was made exposing a Richter's femoral hernia in the left side involving the antimesenteric border of the ileum. No resection was necessary. The sac was excised and the femoral defect repaired. Except for a transient cystitis, the postoperative course was benign and the patient was discharged on the eleventh postoperative day.

CASE 5. C. P., an 89 year old male, was admitted with an 18 hour history of "coffee ground" emesis. He was demented, and no other significant history could be elicited. Physical examination revealed: temperature 38 degrees C., pulse 88 irregular, respiration 22, and blood pressure 190/120. He appeared emaciated, with a slightly protuberant abdomen, and minimal epigastric and left, lower quadrant tenderness. A minimally tender 3 centimeter mass was felt in the left groin. A roentgenogram of the abdomen showed no evidence of obstruction. Significant laboratory findings consisted of hemoglobin 15.0, and white blood count of 51,200 with 70 per cent lymphocytes. The diagnosis of chronic lymphatic leukemia and upper gastrointestinal bleeding was made and the patient was, therefore, admitted to the medical service. The mass in the left femoral area was interpreted as lymphadenopathy secondary to leukemia. Abdominal distention persisted and he again had "coffee ground" emesis which was guaiac positive. On the third hospital day, a gastrointestinal series was done in an effort to locate the site of bleeding. No pathologic change could be demonstrated in the esophagus, stomach, or duodenum. Follow-up films 24 hours later

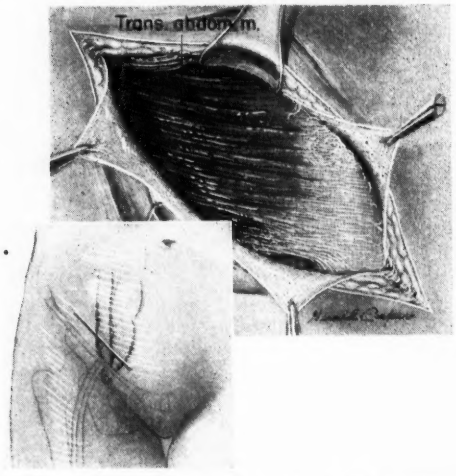


FIG. 1. The inset shows the position of the inguino-abdominal incision placed about 3 centimeters cephalad and parallel to the inguinal ligament. The external oblique fascia has been divided in line with its fibers and the internal oblique muscle has been freed from its attachment to the inguinal ligament and retracted superiorly.

demonstrated barium in distended and fluid filled loops of the small intestine suggesting small bowel obstruction. Surgical consultation was requested and at this time the patient appeared acutely ill, with a distended abdomen, high pitched peristalsis, and a slightly tender 4 centimeter mass in the left femoral area. The diagnosis of small bowel obstruction probably as a result of an incarcerated Richter's femoral hernia was made. A left inguino-abdominal incision was made under local anesthesia and a Richter's femoral hernia was exposed. The edge of the lacunar ligament was incised to free an incarcerated loop of terminal ileum containing a hemorrhagic and obviously infarcted area measuring about 3 centimeters in diameter in its antimesenteric side. A 10 centimeter segment of terminal ileum was resected and continuity was established with an end-to-end anastomosis. The hernial sac was amputated and the femoral defect repaired. The postoperative course was surprisingly benign, and the patient was discharged on the tenth postoperative day.

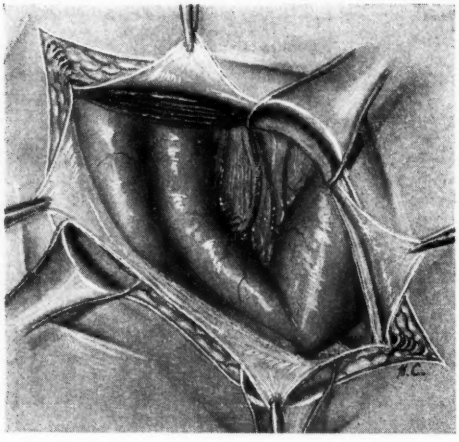


FIG. 2. The transversus abdominis muscle and peritoneum have been incised and the incarcerated femoral Richter's hernia exposed.

CASE 6. R. P., a 5 month old male infant with a known previously easily reducible umbilical hernia was admitted 3 hours after incarceration of the hernia. Vomiting followed soon after incarceration.

On physical examination the infant appeared acutely ill with a temperature of 37.7 degrees C., pulse 110, respiration 40, and a systolic blood pressure of 90. The abdomen was distended and a tense, erythematous, irreducible, umbilical hernia measuring about 4 centimeters in diameter was noted. Significant laboratory studies revealed: hemoglobin 7.2, hematocrit 23, and white blood count 15,200. Under general anesthesia the hernia was exposed through a semicircular incision and on opening the sac a cyanotic knuckle of incarcerated bowel presented. While trying to deliver the bowel for inspection it receded into the abdomen necessitating enlarging the incision and careful inspection of the entire bowel. A small ecchymotic area was found on the anterior aspect of the transverse colon which represented the incarcerated segment. A Mayo type repair of the hernia was carried out. Except for a short period of ileus, the postoperative course was benign and the patient was discharged on the eighth postoperative day.

DISCUSSION

The femoral ring is by far the most common site for a Richter's hernia with the inguinal region next in frequency. Less common sites are in umbilical, incisional, obturator, and epigastric hernias. In fact, there is no reason why a Richter's hernia could not be associated with any other type of internal or external hernia. The terminal ileum is the usual portion of the bowel which becomes strangulated and it is the antimesenteric portion of the wall of the bowel that is involved. The hernial ring is usually small, firm, and with unyielding margins, an important factor in the etiology of this interesting hernia. When the presenting clinical picture is that of a partial intestinal obstruction of obscure etiology, incarceration of a femoral hernia should be suspected even in the absence of a palpable hernia. In 117 cases of Richter's hernia compiled by Governale up to 1941, only 50 per cent had clear manifestations of intestinal obstruction and a

palpable mass in the hernial ring. The incarcerated segment is usually quite small resulting in minimal signs until a sufficiently large portion of the circumference of the bowel is drawn into the sac leading to partial or complete obstruction. About 60 per cent of the patients with Richter's hernia in Frankau's series did not receive treatment until the condition had been present for 48 hours or more. The mild character of the symptoms which often encourage delay or lead to an incorrect diagnosis, and the frequency with which early gangrene and peritonitis occur, are largely responsible for the high mortality rate which accompanies this condition.

The treatment of choice is, of course, operation performed as soon as the patient's condition permits. Very little emphasis has been given to the surgical approach in the previously reported cases. In most instances the incision has been placed directly over the hernial mass. This approach, however, leads to inadequate exposure and inability to examine the bowel properly, and involves the great risk of reducing the strangulated intestine before it can be properly inspected. This complication is reported by Fowler and Gordon, and in each instance a second abdominal incision was needed to determine the viability of the strangulated loop.

The 5 cases of femoral Richter's hernia reported upon were all approached by an inguinoabdominal incision placed about 3 centimeters cephalad and parallel to the inguinal ligament (Fig. 1). The external oblique fascia was divided in line with its fibers, and the underlying internal oblique muscle was dissected free from the inguinal ligament and retracted superiorly. The incision was extended to the peritoneum by incising the transversus abdominis muscle in line with its fibers and ligating the inferior epigastric vessels, thus exposing the underlying incarcerated loop of bowel (Fig. 2). If moderate pressure failed to dislodge the hernia this could be accomplished quite easily by incising the edge of the lacunar ligament (Fig. 3). The bowel was then examined and its viability determined. Some surgeons have advocated inversion of the strangulated area in those instances in which the injured portion is small and sharply localized. However, when one is faced with a strangulated and devitalized portion of bowel it is far safer to resect the involved segment. The hernial sac is easily dealt with by grasping its apex with a clamp and everting it, amputating the excess sac

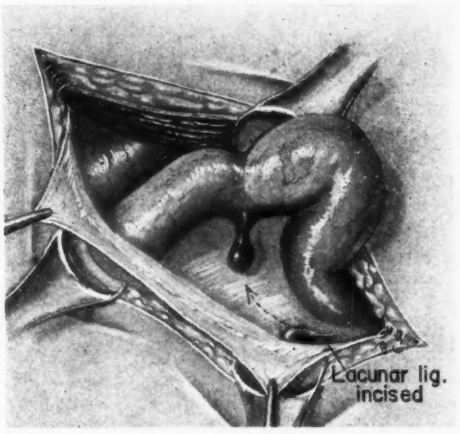


FIG. 3. The incarcerated antimesenteric portion of the bowel has been released after incising the edge of the lacunar ligament.

distal to a purse-string suture. After the incision in the peritoneum and transversalis fascia has been closed and the edges of the transversus abdominis muscle are approximated, repair of the hernial defect is undertaken retroperitoneally utilizing the McVay technique (Fig. 4).

Of the 6 cases of Richter's hernia reported upon 5 were in femoral hernias and 1 was in an umbilical hernia. Three of the fermoral hernias

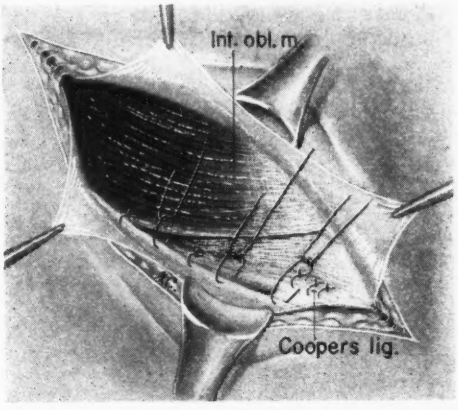


FIG. 4. The peritoneal incision has been closed and the femoral defect is being repaired with interrupted sutures approximating Cooper's ligament to inguinal ligament, transversalis fascia to Cooper's ligament, and conjoined tendon to inguinal ligament.

occurred on the right side and 2 on the left. Except for the 1 case of umbilical Richter's hernia in a 5 months old male infant the youngest patient was 72 years old and the oldest was 89 years old. There were no adhesions in any of these cases between the herniated bowel and the hernial sac similar to those described by White and Gillespie. The only mortality in this group occurred on the eighth postoperative day in a patient with a femoral hernia, probably the result of a pulmonary embolus or of a coronary occlusion.

CONCLUSIONS

1. Six cases of Richter's hernia seen within the period of 1 year are reported. Five of these cases occurred in femoral hernias and 1 in an umbilical hernia.

2. A historic review is presented and the difference between Richter's and Littré's hernias is emphasized.

3. Review of the literature reveals a persistently high mortality rate which is largely due to lack of early recognition. If treatment is not instituted promptly, perforation frequently occurs in the absence of the usual signs of obstruction.

4. The treatment of choice is operation performed as soon as the patient's condition permits.

5. The inguino-abdominal approach is strongly recommended for Richter's hernia occurring in the inguinal and femoral regions. The technique is described in detail.

REFERENCES

1. Bissell, A. H. Richter's hernia. Am. J. Surg., 1929, 7: 864.
2. Cattell, R. B. Richter's hernia. Surg. Gyn. Obst., 1933, 56: 700.
3. Fowler, R. S. Partial enterocele. Ann. Surg., 1899, 29: 533.
4. Frankau, C. Strangulated hernias, a review of 1487 cases. Brit. J. Surg., 1931, 19: 176–191.
5. Gillespie, R. W., Glas, W. H., and Musselman, M. Richter's hernia. Arch. Surg., 1956, 73: 590.
6. Gordon, R. P. Richter's hernia and carcinoma of colon. Lancet, Lond., 1934, 1: 234.
7. Governale, S. L., Markiewicz, S. S., and Rotondi, A. J. J. Internat. Coll. Surgeons, 1941, 4: 160.
8. Littré, Alexis. Observation sur une nouvelle espece de hernie. Hist. Acad. roy. d. sc., Par., 1700, 300–310.
9. Richter, A. G. Abhandlung von den Bruechen. Pp. 597–624. Gottingen: J. C. Dieterich, 1785.
10. Treves, F. Richter's hernia or partial enterocele. Tr. R. Med. Chir., 1887, 52: 149–167.
11. White, C. S. Richter's hernia. Surg. Gyn. Obst., 1914, 14: 45.

THE THORACOABDOMINAL INCISION FOR SURGERY OF RENAL, ADRENAL, AND TESTICULAR NEOPLASMS

B. G. CLARKE, M.D., F.A.C.S., HAROLD A. RUDY, M.D., and
WYLAND F. LEADBETTER, M.D., F.A.C.S., Boston, Massachusetts

A REVIEW of 164 consecutive, unselected cases is presented in which thoracoabdominal incisions were used in operations for tumors of the kidneys or adrenal glands or for removal of primary or metastatic neoplasms of the retroperitoneal structures during the period from 1947 to 1956 at the Massachusetts General and the New England Center Hospitals. The study includes private patients of the authors; patients on house services operated upon by members of the resident staffs; and through the kindness of the authors' colleagues, other private patients at both institutions. Material has been analyzed in terms of: (1) indications and applicability of the thoracoabdominal incision; (2) incidence of nonfatal and fatal complications, and (3) generalizations on operative technique which might be possible on the basis of increasing experience since the detailed and well illustrated description of the operation, as used for tumors, by Chute, Soutter, and Kerr in 1949.

The biologic importance of wide, radical dissection for neoplasms of these organs has recently been discussed by Foley, Mulvaney, Richardson, and Victor. As an aid in obtaining wider exposure to accomplish this, Hess proposed resecting the twelfth rib, and more recently Woodruff has described extrapleural resection of the eleventh rib. Nagamatsu and his associates have devised a dorsolumbar flap incision for the same purpose.

As early as the First World War, Fullerton, studying British military experience, appreciated the potential value of a thoracoabdominal incision for operations on the kidney. By 1930, Constantini and Bernasconi had utilized such an incision successfully in operating upon a hunchbacked patient in whom a flank approach was prevented by the chest deformity. In the succeeding two decades, thoracoabdominal incisions acquired acceptance in surgery of the esophagus, stomach, spleen, adrenal glands, biliary tract, and portal vein.

During the Second World War, Marshall and Wylie, Hoffmann, Williams, and Rose used thoracoabdominal incisions with success in the treatment of kidney wounds. Since the report by Chute, Soutter, and Kerr of their experience in 39 operations for kidney tumors, we have been able to find reports of 11 additional cases in the papers by Mortensen, O'Conor and Head, Robertson and Jameson, and Perez Castro and Gil Turner. Cooper, Leadbetter, and Chute have discussed the thoracoabdominal approach to the retroperitoneal nodes in the radical orchidectomy for cancer of the testis.

Whether or not the new, more radical approaches to renal, adrenal, and retroperitoneal neoplasms will yield increased survival rates remains to be answered by the passage of time. The present study, we believe, indicates that this should prove true and demonstrates the following advantages of the thoracoabdominal incision in the treatment of cancer: (1) It has an acceptably low incidence of operative complications and mortality. (2) As in 2 cases in the present study, it permits safe and complete removal of cancers inoperable by other routes. (3) It allows early interruption of vascular channels to tumor and minimizes the possibility of tumor embolization. (4) It is adaptable in patients with rib cage deformities. (5) It may be used when scarring due to previous multiple flank incisions or x-ray therapy would make dissection through the old scar difficult or hazardous. (6) It allows adequate exposure for en bloc resection of renal or adrenal cancer, encased in the intact adiposofascial investments of these organs and, when indicated, a regional lymphadenectomy. (7) The incision gives sufficient exposure for safe resection, when necessitated by tumor involvement,

From the Departments of Urology, Tufts University School of Medicine, the New England Center Hospital and the Massachusetts General Hospital, Boston.

TABLE I.—LEVEL OF THORACOTOMY

Level	*No.*
Seventh rib	1
Ninth rib	2
Ninth to tenth interspace	4
Tenth rib	72
Tenth to eleventh interspace	24
Eleventh rib	55
Eleventh to twelfth interspace	4
Twelfth rib	2
Total	164

TABLE II.—TYPES OF PRIMARY OPERATIONS

Types	*No.*
Nephrectomy	94
Resection of renal cyst or of renal, adrenal or retroperitoneal tumor	40
Node dissection for cancer of testis or epididymis	25
Biopsy only	2
Exploration only	2
Pyelolithotomy	1
Total	164

TABLE III.—SIMULTANEOUS, MAJOR PROCEDURES IN ADDITION TO PRIMARY OPERATION

Operations	*No.*
Regional lymphadenectomy for renal or adrenal tumor	32
Adrenalectomy, total or partial	14
Splenectomy	9
Nephrectomy	7
Partial hepatectomy	6
Partial pneumonectomy	6
Partial pancreatectomy	3
Partial colectomy	3
Appendectomy	3
Sympathectomy	3
Ureterectomy	2
Segmental resection of vena cava	2
Partial cystectomy	1
Oophorectomy	1
Esophagogastrectomy, first stage	1
Cholecystectomy	1
Total	94

TABLE IV.—COMPLICATIONS

	Nonfatal cases	*Fatal cases*	*Table V, Case No.*
Pulmonary			
Atelectasis	9	1	3
Pulmonary infarction	1	1	1
Pulmonary edema		1	7
Cardiovascular-renal			
Hypotension	5		
Hypotension, anuria		1	5
Hypotension, uremia, gastric hemorrhage		1	4
Myocardial infarction	1	2	6, 8
Systemic			
Unexplained fever	3		
Transfusion reaction	2		
Drug reaction	2		
Cachexia, hepatic metastases		1	2
Local			
Ileus	9		
Pleural effusion	8		
Wound sepsis	6		
Wound hematoma	2		
Incisional hernia	1		
Painful incision	1		

of the great vessels, of adjacent viscera within the pleural or peritoneal cavities, or of local tumor extension to retroperitoneal structures, diaphragm, or muscular parietes. (8) It is an excellent approach for radical retroperitoneal lymph node dissection in cases of cancer of the testis or epididymis.

MATERIAL

One hundred and sixty-four patients were studied. Their average age was 53 years, with a range from 4 to 84 years. One hundred and twenty patients were males, 44 females. Lesions occurred on the right side in 79 patients, on the left in 85.

One hundred and eight operations were done for renal masses. Sixty-eight were renal cell carcinomas; 5 transitional cell or papillary carcinomas of kidney or kidney pelvis; 4 embryonal or Wilms type cancers (2 in adults, 1 in a child of 4, and 1 in a child of 5); 1 a hamartoma; 1 an adult teratoma; and 29 solitary serous cysts of the kidney. Twenty-five operations were undertaken for removal of regional lymph nodes in cancer of the testis; 2 in cases of epididymal cancer. Thirteen patients had operations for various types of nonmalignant renal disease. Ten operations were done for adrenal tumors or hyperplasias; 6, for retroperitoneal tumors.

In 72 patients the tenth rib was resected subperiosteally; in the others intercostal incisions or subperiosteal rib resections were carried out, as indicated, at levels from the seventh to the twelfth rib (Table I). In only 13 patients was it necessary after operation to leave a catheter in the chest attached to suction or water-sealed drainage. This was done if frank sepsis had been encountered, if the lung had been opened or partly removed, or if for technical reasons oozing of blood or serum into the pleural cavity might have been anticipated after operation. Drains were left in the retroperitoneal soft tissues, for various reasons, in 10 cases.

Postoperative care did not differ from that given after any type of major, uncomplicated thoracic or abdominal operation. Use of oxygen was rarely necessary. A roentgenogram of the chest was made 3 to 4 hours after operation to assure that the lung was satisfactorily re-expanded, that no tension pneumothorax was present, and that no zones of atelectasis persisted. Patients usually left the hospital 7 to 10 days after operation, some as early as 4 days.

TABLE V.—ANALYSIS OF HOSPITAL MORTALITY

Case	*Initials*	*Age Sex*	*Day of death*	*Side*	*Diagnosis*	*Operation*	*Remarks*	*Cause of death*	*Autopsy*
1.	G. Hal.	47 M	5	R	Hamartoma kidney	Nephrectomy; Reginal lymphadenectomy		Pulmonary infarction	No
2.	H. Pom.	52 M	27	L	Renal cell carcinoma	Nephrectomy	Wound abscess explored and drained 16th day	Hepatic metastases	No
3.	M. Dav.	60 F	2	L	Renal cell carcinoma	Nephrectomy	Obese (360 lb.), hypertensive	Atelectasis	No
4.	D. Alb.	61 M	28	R	Renal cell carcinoma	Nephrectomy; regional lymphadenectomy	Hypotension; azotemia, gastric hemorrhage from acute ulcers, gastrectomy 20th day, dehiscence of wound 28th day	Wound dehiscence, renal tubular necrosis	Yes
5.	F. Sch.	62 M	3	R	Renal cell carcinoma	Nephrectomy	Avulsion renal vein, suture vena cava, 4500 c.c. transfusion, hypotension	Anuria	No
6.	G. Cal.	63 M	14	L	Renal cell carcinoma	Nephrectomy		Myocardial infarction	No
7.	D. Per.	72 F	4	L	Stone	Pyelolithotomy	Scoliotic; postoperative retroperitoneal abscess	Atelectasis; pulmonary edema	No
8.	D. Mar.	77 M	9	L	Embryonal carcinoma of kidney	Nephrectomy, regional lymphadenectomy, splenectomy, left colectomy, transverse and sigmoid colostomy	Cachectic	Myocardial infarction	No

RESULTS

Table II shows that in 160 of 164 patients operation was carried out as planned. In 2 patients biopsy only was feasible and in 2 others exploration alone was performed. Nine of the 25 node dissections for cancer of testis or epididymis yielded cancer in the nodes.

Tumors were removed which ranged in maximum diameter from 3 to 27 centimeters, with an average size of 12 centimeters.

Table III shows that the incision can be successfully used in the attack not only upon locally invasive cancer in adjacent viscera but upon concurrently existing disease in other organs within the chest or abdomen. Ninety-four additional, simultaneous major procedures (Table III) were performed as well as the primary procedures listed in Table II.

The selection of absorbable or nonabsorbable suture material for closure had no discoverable effect upon results.

Complications are summarized in Table IV. Eight patients died in the hospital (Table V). The hospital mortality rate was 4.9 per cent.

Analysis of complications indicates that they were the result not of the type of incision but were the complications, generally, of extensive operations for cancer in elderly and often depleted patients. Among the 29 patients, whose average age was 57 years, from whom renal solitary cysts were removed there were no deaths. The only complications were unexplained fever in 1 case and incisional hematoma in 1 case. Twenty-seven patients, with an average age of 37 years in contrast with the average for the entire group of 164 patients of 53 years, underwent retroperitoneal lymph gland dissection for cancer of the testis or epididymis. In this group of younger patients there were also no deaths and few complications. In 2 patients pleural effusions developed; in 2, wound infections; and in 1, atelectasis.

Of particular interest were the 2 patients whose kidney cancers were satisfactorily removed thoracoabdominally after a previously unsuccessful attempt at nephrectomy through a flank incision. A 46 year old man with cancer of the left kidney is an example. A flank opera-

tion had been attempted elsewhere in February 1952. The kidney tumor was biopsied and declared inoperable. Urinary bleeding persisted. Study disclosed no metastases and on August 9, 1952 a thoracoabdominal operation was done, and the kidney, spleen, part of the diaphragm, and the tail of the pancreas were removed. Convalescence was uneventful and the patient has survived, apparently well, until the present. It is our opinion that no kidney cancer should be considered inoperable until exploration has been undertaken by the thoracoabdominal route.

DISCUSSION

Adequate descriptions of the technique have appeared elsewhere but a few technical considerations merit review in view of accumulating experience. The usual kidney position is satisfactory and can be obtained, if special equipment is lacking, by use of sandbags and straps. A large needle should be secured in a vein and blood be available for transfusion. Blood loss should be estimated during the progress of operation; this can be done by weighing sponges and measuring aspirated blood. Endotracheal anesthesia is used.

Subperiosteal rib resection has certain advantages over an intercostal incision: (1) If periosteum is preserved and the pleural incision not extended beyond the cut stump of rib a strong and accurate pleuroperiosteal reconstruction can be made. (2) Preservation of intercostal neurovascular bundles is easy during extension of the incision, abdominally, between them. (3) Healing is remarkably free of pain. (4) Resection of a short anterior segment of rib allows easy access to the retroperitoneum for exploration if the differential diagnosis between renal cyst or tumor is in doubt; if tumor is found, it can be treated by extending the incision for radical nephrectomy.

Alternatively, if the diagnosis of cyst or tumor is in doubt, the kidney can be exposed through the abdominal component of the incision which may later be extended transthoracically. This approach has the advantage of permitting intraperitoneal exploration through a limited incision before the operator is committed to extensive dissection.

If cancer is encountered, any opening made in Gerota's fascia for exploration may be repaired and en bloc resection begun. The kidney is left within its intact fascial investments which are stripped cleanly from psoas, quadratus, diaphragm, and peritoneum. If the peritoneum is adherent to the lesion it is resected with the specimen. Later reconstruction of the peritoneum is not essential.

Large collateral vessels, commonly found, are seen easily through the incision and interrupted as the operation progresses to minimize tumor spread and blood loss. As early as possible, the renal pedicle is exposed and secured. Though in theory the vein should first be sectioned, we have found that engorgement of the kidney and excess blood loss are prevented if the artery is first interrupted and the vein tied separately a few seconds later.

Regional lymphadenectomy for renal cancer is not practicable until removal of the kidney. Standard instruments and sutures for blood vessel reconstruction should be available. Dura clips are useful for fine vessels. For control of larger vessels bulldog, Satinsky, and other types of clamps are employed. In 2 patients of the present series, segments of vena cava were resected below the remaining renal vessel without important undesirable sequelae.

At some stage of operation, exploration of peritoneal and pleural cavities is usually indicated. Of interest in the present group of cases was the finding by this means in several patients of palpable metastatic mediastinal or pulmonary tumor nodules undiscovered in preoperative roentgenograms. In suitable cases, resection of accessible pulmonary masses may be required for biopsy or in the attempt at cure.

During closure, mattress sutures can be used satisfactorily for repair of the diaphragm, with a separate layer of fine stitches to close the diaphragmatic pleura if necessary.

Closure of the wound is in layers and as far as we could discover the type of suture material selected had no effect on results. A retroperitoneal soft tissue drain may be left in the incision if indicated. At the end of operation the lung is re-expanded and air either aspirated from, or expelled by positive pressure through, a catheter in the pleural cavity. The indications for leaving this attached to suction or drainage after operation or withdrawing it immediately after re-expansion of the lungs have been discussed.

SUMMARY

Through a thoracoabdominal incision, 164 operations were done for removal of disease,

chiefly malignant, of the kidneys, adrenal glands, and retroperitoneal structures or for radical resection of regional lymph nodes in cases in which tumor was primary in the testis or epididymis. In addition to the 164 primary operative procedures, it was possible to carry out through the same incisions 94 additional, simultaneous major operative procedures on the great vessels or structures within the pleural or peritoneal cavities or retroperitoneal space indicated by tumor extension or presence of concurrent though unrelated major pathologic conditions.

The hospital mortality rate was 4.9 per cent. The incidence of nonfatal complications was low and appeared to be related chiefly to extensive cancer surgery in elderly, often depleted patients rather than to the incision itself. In 29 patients in whom solitary cysts were discovered and among the 27 younger patients undergoing retroperitoneal node dissections for testicular or epididymal cancer, there were no deaths and few complications.

The thoracoabdominal incision, performed under endotracheal anesthesia, permits en bloc resection of tumor-containing structures within their intact adiposofascial investments, and a satisfactory attack on extension of disease to the great vessels, retroperitoneal lymph nodes, and adjacent viscera. It is adapted to use in patients in whom rib cage deformities or in whom extensive scarring due to previous operations or x-ray treatment would make operation through another route difficult or impossible. It allows early interruption of vascular channels to minimize tumor spread during operation, and permits satisfactory removal of tumors inoperable by other routes. No kidney cancer should be considered inoperable until exploration has been undertaken through a thoracoabdominal incision.

REFERENCES

1. CHUTE, R., SOUTTER, L., and KERR, W. S. The value of the thoracoabdominal incision in the removal of kidney tumors. N. England J. M., 1949, 241: 951-960.
2. CONSTANTINI and BERNASCONI. Presse méd., 1930, 22: 376. Loc. cit. (11).
3. COOPER, J. F., LEADBETTER, W. F., and CHUTE, R. Thoracoabdominal approach for retroperitoneal gland dissection; its application to testis tumors. Surg. Gyn. Obst., 1950, 90: 486-496.
4. FOLEY, F. E. B., MULVANEY, W. P., RICHARDSON, E. J., and VICTOR, I. Radical nephrectomy for neoplasm. J. Urol., Balt., 1952, 68: 39-49.
5. FULLERTON, A. Wounds of the urinary organs. (British) History of the Great War Based on Official Documents. Medical Services: Surgery of the War. Vol. I, pp. 551-567. London: His Majesty's Stationery Office, 1922.
6. HESS, E. Resection of the rib in renal operations. J. Urol., Balt., 1939, 42: 943-949.
7. MARSHALL, D. F. Urogenital wounds in evacuation hospital. J. Urol., Balt., 1946, 55: 119-132.
8. MORTENSEN, H. Transthoracic nephrectomy. J. Urol., Balt., 1948, 60: 855-858.
9. NAGAMATSU, G. R., LERMAN, P. H., and BERMAN, M. H. The dorsolumbar flap incision in urologic surgery. J. Urol., Balt., 1952, 67: 787-803.
10. O'CONOR, V. J., and HEAD, J. R. Transthoracic nephrectomy (left) for Wilms' tumor. J. Urol., Balt., 1951, 65: 193-196.
11. PEREZ CASTRO, ENRIQUE, and GIL TURNER, CARMELO. Nefrectomia transtoracica. Arch. españ. urol., 1952, 8: 97-128.
12. ROBERTSON, J. P., and JAMESON, S. Thoraco-abdominal nephrectomy. J. Urol., Balt., 1952, 67: 585-597.
13. WOODRUFF, L. M. Eleventh rib; extrapleural approach to kidney. J. Urol., Balt., 1955, 73: 183-188.
14. WYLIE, R. H., HOFFMANN, H. L., WILLIAMS, D. B., and ROSE, W. F. Thoracoabdominal casualty. Ann. Surg., 1946, 124: 463-487.

CONTINUOUS, AUTOMATIC, ELECTRONIC DETERMINATIONS OF OPERATIVE BLOOD LOSS

HARRY H. LeVEEN, M.D., and JEANETTE L. RUBRICIUS, M.D., Brooklyn, New York

THERE IS A DEFINITE NEED for a simplified method by which operative blood loss can be accurately determined. With the extension of the surgical horizons, greater operative blood losses have been encountered and vital signs cannot and should not be fully depended upon as indications for adequacy of blood replacement. An important reason that one cannot rely on vital signs is that overtransfusion will produce a syndrome which is not unlike that of shock with a fall in blood pressure and a rapid pulse. Besides, thoracic surgery, heart surgery, vascular surgery, hypothermia, anoxia, hypercapnia, replacement of the heart with pumping mechanisms during surgery, and a host of other artificial situations sometimes mask the vital signs.

More important is that physiologic changes should not be relied upon as an indication of a blood deficit since undesirable alterations have already occurred when they are detected. Changes in hemodynamics demonstrate that compensatory mechanisms have failed and that homeostasis no longer exists. It is during these critical moments that ventricular fibrillation ensues, liver damage takes place, cerebral anoxia occurs, and vessels undergo thrombosis. Ideally, blood should be continuously replaced at a rate which equals the loss. This fundamental precept of blood replacement requires a method of blood loss measurement that is instantaneous, continuous, accurate, and reliable. A method is described which fulfills these rigid requirements.

Several methods are available for determining blood volume preoperatively and postoperatively, and these methods have a fair degree of accuracy. The dilution procedures utilizing Evans blue or radioactive iodinated protein are the most commonly employed. More recently, radioactive red blood cells (tagged with chromium or iron) have been applied to this problem. These methods, however, have shortcomings in that they are not suitable for determining second-by-second and minute-by-minute losses. In addition, the dilution methods are highly inaccurate in situations such as shock. They are little aid, therefore, for the immediate management of the operative patient.

There are two techniques which are adaptable to the requirements of the operative state. As Baronofsky and his associates have stated, these depend on the constancy of blood hemoglobin and specific gravity. In the hemoglobin method, the blood is diluted with a known quantity of water usually contained in a tub or washing machine. The change in the hemoglobin increment is directly proportional to the amount of blood added. The hemoglobin method is based on the assumption that the hemoglobin concentration in the circulating blood is constant at approximately 15 grams. Some use the hemoglobin concentration at the beginning of the operation. Variations of one-third in the hemoglobin level are possible without seriously impairing vital body function but it would produce gross errors in estimation of the amount of blood loss. In addition, the error is in the direction which indicates that the blood loss is less extensive. Aside from this basic defect, there are serious technical inaccuracies in the method. The alkaline hematin changes on standing. Fat is extracted from bloody sponges and from tissue interfering with the optical density (light transmission) so that errors are introduced in the hemoglobin determinations. The hemoglobin may not be completely extracted from clots. Lint and other substances also interfere with the optical densities. It is, therefore, apparent that the hemoglobin method, although cumbersome, could be adapted for minute-to-minute studies but the method is subject to a high degree of inaccuracy.

The gravimetric method is based on the fact that 1 cubic centimeter of blood weighs approximately 1 gram. The greatest variation in

From the Departments of Surgery of the Veterans Administration Hospital, Brooklyn, New York, and of the State University of New York, Downstate Medical Center, Brooklyn, New York.

specific gravity of corpuscles runs from 1.024 to 1.0380 with an average of 1.0293. The specific gravity of the plasma varies from 1.0253 to 1.0287 with an average of 1.0270. Previously weighed dry sponges are used at the time of surgery and sponges are weighed during the operation, the difference in weight between the dry sponge and the bloody sponge being taken as the weight of blood. This method is very difficult to use since it requires extra operating room personnel and since the blood loss when brisk is often taken up in a suction bottle. Although the specific gravity of the blood itself does not vary appreciably, the method is subject to error since the bloody sponges occasionally dry out between weighings unless the weighings are made almost immediately. In prolonged procedures, the evaporative loss can be considerable. In addition, a large error resides in the fact that multiple small weighings are done. A difference of 1 gram in 20 grams introduces a sizable error and these errors are cumulative. If wet sponges are used occasionally, a considerable error results. When hemorrhage is profuse, time is lost in collecting the sponges, weighing, and making the necessary calculations. During these periods of emergency, operating room personnel are often busy elsewhere. Habif has critically evaluated the gravimetric method and concludes that it is susceptible to considerable inaccuracy. It is cumbersome, unwieldy, time-consuming, and is not suitable for measuring the rapid blood loss. It cannot be adapted for use in obstetrics. Instead of weighing, the change in specific gravity caused by the addition of blood to water can be adapted to measure blood loss. The disadvantages are similar to those of the hemoglobin method since anemia and hypoproteinemia will result in a reduction in the specific gravity of blood. Lint, foam, and fat interfere with specific gravity determinations. A need therefore exists for a rapid, simplified, accurate method for the operative and obstetric determination of blood loss which will lend itself to automatic recording techniques so that operating room personnel will not be involved and instantaneous tallies on the extent of blood loss will always be available.

This article presents a method which meets the requirements mentioned. This method depends on the fact that the blood is an electrolyte solution of constant composition which does not vary greatly even in serious diseases in which blood electrolytes are known to be altered. Even in abnormal states such as low salt syndrome, the variation is usually not greater than 15 per cent of normal serum values, "a reduction of 15 to 20 milliequivalents per liter," as stated by Leiter and associates. The specific conductivity of blood depends upon the electrolyte concentration and has a fairly constant value. Conductivity will accurately measure extremely small quantities of sodium chloride in solution. As shown in a previous article, the conductivity method made possible the precise determinations of sodium chloride in 1:1000 diluted sweat (5). It was this application which suggested the use of conductivity in the measurement of operative blood loss. The practicality of utilizing the conductivity of whole blood as a method for determining operative blood loss is the subject of this investigation.

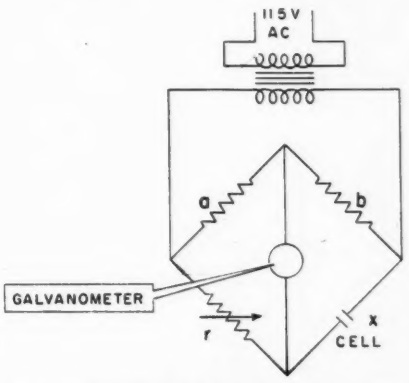


FIG. 1. The usual form of a Wheatstone bridge is illustrated. No provision has been made for temperature compensation. In the diagram the variable resistance used to bring the galvonometer into null balance is labeled *r*. The resistance of the conductivity cell is labeled *X* and fixed resistances are labeled *a* and *b*. Accordingly: $\frac{b}{a}=\frac{X}{r}$. Then: $X=\frac{b}{a}r$.

MATERIALS AND METHODS

If two metal plates are immersed in a salt solution, a current will flow when the plates are connected to an electrical power supply. The ions carry electrons to the positive pole. The quantity of electricity which passes between the plates (electrodes) can be calculated from Ohm's law, i.e., $E=RI$, where E is the potential difference measured in volts, R is the resistance measured in ohms, and I is the current measured in am-

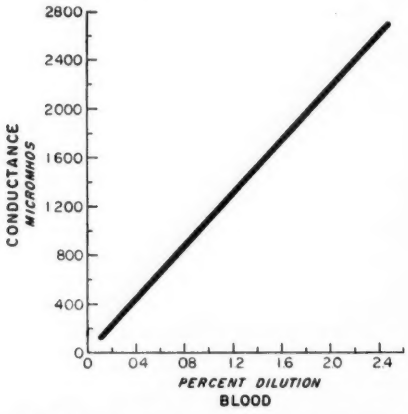


FIG. 2. Relationship between conductance in micromhos and percentage of blood in solution using distilled water as the diluent.

peres. As the salt concentration of a solution increases, the resistance of the solution to the passage of current decreases. The conductivity is said to increase since conductance is the opposite of resistance. Actually, conductance (measured in mhos) is the reciprocal of resistance (measured in ohms), $\text{MHO} = \frac{1}{\text{OHM}}$. Conductivity can be measured with a Wheatstone bridge of an alternating current type which is referred to as a conductivity bridge. In one arm of this conductivity bridge is a calibrated cell which dips into the solution. As the electrolyte concentration increases, the electrical resistance across the electrodes of this cell decreases. By balancing the bridge, the changing resistance of this cell is measured (Fig. 1). This measurement can be expressed in solution conductance (mhos) or in resistance (ohms). In the early phases of the study, conductivity was measured with a manual type conductivity bridge and a dip or Henry type of conductivity cell. Twenty independent determinations on a single specimen showed that there was less than a 2 per cent variation between the most divergent results. These values attest the high degree of sensitivity and accuracy of the method since a proportion of the error can be attributed to pipetting and dilution. The blood samples of 55 ambulatory ward patients selected at random were almost identical (Table I). Fifty-one of 55 samples (93 per cent) had deviations of less than 3 per cent and in 44 of 55 (80 per cent), the deviation was less than 2 per cent. The mean deviation is 1.3 per cent. The greatest deviation of any 1 sample from the mean was less than 5 per cent. This showed that the method was subject to a high degree of accuracy with respect to the basic concept of the constancy of blood conductivity.

The blood was uniformly diluted with tap water or distilled water in making these measurements. Initially, the conductivity of the water was subtracted from the observed conductivity of the diluted blood to give a corrected reading. In later studies, it was found more precise to use tap water of low conductivity or distilled water. Then, the initial blank value need not be subtracted. When blood is diluted with tap water or distilled water and the change in conductivity is measured, it is found to follow a relatively linear relationship to the amount of blood which is added (Fig. 2). For the purpose of calibration and calculation, the conductivity of 55 random specimens of diluted and hemolyzed blood was found to be equivalent to .65 per cent sodium chloride (Table I). Also, the conductivity of blood in varying dilutions parallels that of sodium chloride or potassium chloride. These latter values can be obtained from the International critical tables.

After these preliminary experiments, an automatic blood loss instrument was constructed. It calculates and instantaneously registers the blood loss even when the blood is clotted or has

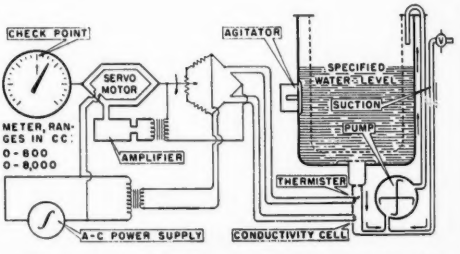


FIG. 3. Schematic diagram of the automatic blood loss meter. A measured volume of distilled water (25,000 c.c.) is added to the tub. An agitator extracts electrolytes from the sponges, lap pads, and clots. A suction apparatus transfers blood from the operative site to the tub. Automatic temperature compensation is accomplished with a thermistor which forms one arm of this bridge. The conductivity cell is also shown. A servomotor continuously keeps the bridge at the null balance point. The dial of the meter is calibrated directly in cubic centimeters of blood. Sponges and laparotomy pads are held in a stainless steel basket indicated by broken line inside container.

been absorbed into laparotomy pads and sponges. The apparatus consists of a large stainless steel tub with an agitator which continuously extracts the electrolytes from the sponges and clots. A suction pump transfers blood from the operating table directly into the tub. This procedure makes possible the addition of blood loss taken up via suction as well as from bloody sponges. Since conductivity increases with increasing temperature of the solution, automatic temperature compensation was accomplished by introducing a thermistor into one arm of the conductivity bridge. The thermistor assumes the temperature of the water in the reservoir and changes the resistance of one arm in the bridge to compensate for the decreasing resistance of the solution at increased temperatures. It was desirable to have a direct reading instrument which would obviate the difficulties of manually balancing the conductivity bridge. Hence, a servomechanism was coupled with the conductivity bridge. The servomotor continuously brings the bridge to the null balance point. Instantaneous and continuous detection of conductivity changes are made. The conductivity bridge and cell must be specially constructed to operate on low voltages in order to minimize polarization and, at the same time, maintain its sensitivity. All components of the machine are constructed to meet explosion proof requirements for use in an operating room. The bridge is calibrated in cubic centimeters of blood rather than in mhos. Blood loss is measured in increments of 100 cubic centimeters up to 8,000 cubic centimeters. A centrifugal pump empties the tub following usage and the tub can be rapidly emptied into a regular sink and refilled so that losses greater than 8,000 cubic centimeters can be measured (Fig. 3). The machine is cleaned with a chlorinated detergent following use and rinsed with tap water. A stainless steel measure is used to measure the initial quantity of tap water placed in the tub. Fixed resistances with push buttons are included so that the calibration of the machine can be pre-tested before use. A null balance of 0 cubic centimeters of blood is automatically accomplished by using tap water of low conductivity or distilled water.[1]

[1]In Albuquerque, N. M., tap water has an electrolyte concentration as great as a 1 to 10 dilution of blood in distilled water. In such situations, the initial reading of the tap water is so high that it exceeds several hundred c.c. of blood. If a quantity of water equal to the initial indication is added to the starting amount, subsequent dilutions will not be in error. Then, the indicated initial blank in c.c. of blood may be subtracted from the total.

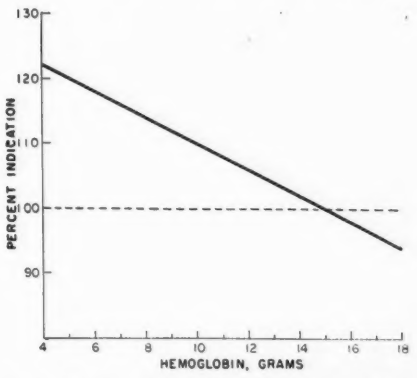


FIG. 4. An automatic correction for anemia is inherent in the method. The blood loss in a patient with an anemia of 7.5 grams (about 50 per cent of normal) would indicate as 115 cubic centimeters. This would lead to an overtransfusion of 15 per cent. The mild overtransfusion ceases when the hemoglobin is restored toward normal.

Correction for the initial conductivity of the water is then unnecessary.

DISCUSSION

From the foregoing, it is evident that sodium chloride solutions cannot be used for irrigation purposes or to moisten laparotomy pads unless a definite measure of the amount of sodium chloride used is made and subtracted from the final total of indicated blood loss. We use small quantities of 2½ per cent glucose for moistening laparotomy pads. Since glucose is a nonelectrolyte, it does not interfere with the readings. Although 25 to 50 cubic centimeters of additional fluid may be added to the tub by such a procedure, the error introduced is exceedingly small when one considers that 50 cubic centimeters is but a small fraction of the initial 25,000 cubic centimeters of water used as a starting fluid. In situations in which large amounts of pleural or ascitic fluid are encountered, a separate suction device should be used to empty these cavities of fluid since the blood loss meter cannot distinguish between these fluids and blood. The errors introduced by added gauze sponges and laparotomy pads have also been measured. The residual amount of soap and electrolyte left in one laparotomy pad following washing in tap water of exceedingly high salt content is equivalent to only 1 cubic centimeter of blood. Also, 100 commercial gauze sponges produced no

TABLE I

Patient	*Reg. No.*	*Hemoglobin*	*Diagnosis*	*Calculated specific conductivity*	*KCL equivalent, meq./L.*	*Specific conductivity deviation*	*Per cent deviation*
G.B.	67151	14.2	Plastic surgery	12.80×10^{-3}	92.8	$-.05\times10^{-3}$	−0.39
E.R.	67215	15.8	Hernia	12.52×10^{-3}	91.8	$.23\times10^{-3}$	1.80
R.S.	66897	14.2	Ethmoidectomy	12.80×10^{-3}	92.8	$-.05\times10^{-3}$	−0.39
R.T.	66966	15.8	Blind	12.74×10^{-3}	93.4	$.01\times10^{-3}$	0.07
I.M.	66955	16.0	Cataract	12.58×10^{-3}	92.2	$.17\times10^{-3}$	1.33
W.D.	67210	16.8	Mobilization of stapes	12.30×10^{-3}	90.0	$.45\times10^{-3}$	3.53
L.L.	66103	14.4	Hernia	12.80×10^{-3}	92.8	$-.05\times10^{-3}$	−0.39
A.K.	67218	15.2	Pilonidal cyst	12.68×10^{-3}	93	$.07\times10^{-3}$	0.55
S.J.	67274	16.1	Hernia	12.60×10^{-3}	92.4	$.15\times10^{-3}$	1.18
C.V.	67356	12.5	Backache	13.08×10^{-3}	96.3	$-.33\times10^{-3}$	−2.58
J.DeG.	67438	14.8	Stasis ulcer	12.76×10^{-3}	93.6	$-.01\times10^{-3}$	−0.07
M.K.	66500	15.4	Laminectomy	12.56×10^{-3}	92.0	$.19\times10^{-3}$	1.47
T.G.	66726	15.6	Fracture	12.90×10^{-3}	94.6	$-.15\times10^{-3}$	−1.18
H.F.	64883	16.0	Accident	12.70×10^{-3}	93.2	$.05\times10^{-3}$	0.39
D.L.	63133	12.1	Nerve palsy	12.92×10^{-3}	94.8	$-.17\times10^{-3}$	−1.33
W.K.	66723	14.8	Plastic surgery	12.76×10^{-3}	93.6	$-.01\times10^{-3}$	−0.07
A.K.	67433	16.2	Subcut. cyst	12.40×10^{-3}	90.8	$.35\times10^{-3}$	2.74
H.R.	64410	16.0	Graft	12.72×10^{-3}	93.2	$.03\times10^{-3}$	0.24
L.P.	66956	15.2	Varicose ulcer	12.68×10^{-3}	93	$.07\times10^{-3}$	0.55
L.D.	67096	14.0	Bilateral stasis ulcer	12.82×10^{-3}	94	$-.07\times10^{-3}$	−0.55
J.DuB.	67067	12.1	Bilateral inguinal	13.24×10^{-3}	97.6	$-.49\times10^{-3}$	−3.84
G.S.	66780	13.8	Pilonidal cyst	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
H.L.	67180	13.5	Papillomas	13.12×10^{-3}	96.4	$-.37\times10^{-3}$	−2.90
J.B.	67216	14.4	Foreign body	12.74×10^{-3}	93.4	$.01\times10^{-3}$	0.07
M.P.	67232	15.8	Pilonidal cyst	12.92×10^{-3}	94.8	$-.17\times10^{-3}$	−1.32
R.H.	67221	14.4	Hernia	12.68×10^{-3}	93	$.07\times10^{-3}$	0.55
A.R.	Techn.	15.6	Normal	12.40×10^{-3}	90.8	$.35\times10^{-3}$	2.74
E.M.	Techn.	13.2	Normal	13.16×10^{-3}	96.6	$-.41\times10^{-3}$	−3.13
E.K.	Techn.	14.8	Normal	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
G.F.	Techn.	15.0	Normal	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
S.D.	67142	14.8	Subcutaneous cyst	12.56×10^{-3}	92.0	$.19\times10^{-3}$	1.47
F.P.	67165	13.2	Hernia	13.10×10^{-3}	96.2	$-.35\times10^{-3}$	−2.74
B.L.	67227	13.2	Umbilical sinus tract	12.70×10^{-3}	93.2	$.05\times10^{-3}$	0.39
J.T.	67313	15.2	Polyps	12.68×10^{-3}	93.0	$.07\times10^{-3}$	0.55
A.Z.	Techn.	15.2	Normal	12.52×10^{-3}	91.8	$.23\times10^{-3}$	1.80
J.W.	Techn.	14.4	Normal	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
H.A.	Empl.	14.0	Normal	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
C.H.	Empl.	16.8	Normal	12.20×10^{-3}	89.4	$.55\times10^{-3}$	4.32
V.C.	Empl.	16.2	Normal	12.58×10^{-3}	92.2	$.17\times10^{-3}$	1.33
W.O'B.	67230	15.2	Free body in knee	12.92×10^{-3}	94.8	$-.17\times10^{-3}$	−1.33
W.A.	67376	14.4	Retracted stump	12.80×10^{-3}	94.0	$-.05\times10^{-3}$	−0.39
L.H.	67052	13.0	Herniated disc	13.04×10^{-3}	95.8	$-.29\times10^{-3}$	−2.27
W.H.	64997	14.8	Skin graft	12.88×10^{-3}	94.6	$-.13\times10^{-3}$	−1.02
V.D.	67443	15.8	Ulcerated toe	12.68×10^{-3}	93.0	$.07\times10^{-3}$	1.33
E.S.	67021	13.8	Ruptured tendon	12.82×10^{-3}	94.0	$-.07\times10^{-3}$	−1.33
W.M.	66757	14.8	Osteomyelitis	12.90×10^{-3}	94.6	$-.15\times10^{-3}$	−1.18
S.H.	67296	12.8	Lacerated tendon	13.04×10^{-3}	95.8	$-.29\times10^{-3}$	−2.27
L.P.	45087	14.4	Fractured tibia	12.80×10^{-3}	94.0	$-.05\times10^{-3}$	−0.39
D.C.	65189	16.0	Excision, radical, right hand	12.50×10^{-3}	91.6	$.25\times10^{-3}$	1.96
J.G.	67461	16.1	Sciatic neuritis	12.60×10^{-3}	92.4	$.15\times10^{-3}$	1.18
C.F.	67057	16.1	Medial tear meniscus	12.50×10^{-3}	91.6	$.25\times10^{-3}$	1.96
C.B.	67129	15.8	Herniated disc	12.62×10^{-3}	92.4	$.13\times10^{-3}$	1.02
R.M.	63602	14.6	Spinal fusion	12.80×10^{-3}	94.0	$-.05\times10^{-3}$	−0.39
J.A.	67129	13.3	Herniated disc	12.84×10^{-3}	94.2	$-.09\times10^{-3}$	−0.71
H.P.	53283	16.1	Amputee	12.60×10^{-3}	92.4	$.15\times10^{-3}$	1.18
Mean	—	—	—	12.75×10^{-3}	93.5	+.166	+1.3

change in the conductivity of the solution. For this reason, it is apparent that no errors are introduced from the gauze materials. The blood loss meter assesses blood loss with a much higher degree of precision than is generally exercised when blood is withdrawn from a donor. The quantity of blood which is let from the donor may vary from 425 to 575 cubic centimeters, yet it is usually counted as a gain of 500 cubic centimeters to the recipient. Spillage or wastage is rarely considered in the summation of the total. If an error of 7.5 per cent can occur in calculating the amount received, inaccuracies in the estimation of loss must be kept to a minimum so that overtransfusion or undertransfusion can be avoided.

Serum conductivity has been shown to decrease approximately 2 per cent for each gram increase in serum protein (when serum protein is measured in grams per 100 cubic centimeters). Since patients undergoing surgery have their plasma protein values restored preoperatively, one rarely sees a patient who has a serum protein of less than 6 grams per 100 cubic centimeters. It is interesting that an error toward hyperproteinemia would lead to a slight overtransfusion (2 per cent per gram hyperproteinemia) since the blood loss measurement would appear by conductivity to be somewhat higher.

Gram states that the ratio of conductivity of serum to whole blood is roughly 2.5 depending upon the packed cell volume. We have found that the conductivity of hemolyzed blood does not follow such coarse variations and marked fluctuations in random samples do not occur. It is possible that the red cell envelope has a higher resistance than the rest of the cell and, hence, changes the conductivity of whole blood. Since hemolysis begins at .45 per cent sodium chloride and is completed at .30 per cent sodium chloride, the dilutions have been so chosen that hemolysis is always complete. Because protein depresses the conductivity values, reduced hemoglobin concentrations would cause increased conductivity values. This situation would register as increased blood loss and the deficit would tend to be corrected.

However, hemoglobin, since it is a protein, interferes with conductivity as does serum protein. This interference has proved to be one of the paragon features of the conductivity method because it automatically compensates for anemia. An anemia of 50 per cent (7.5 gm./1,000 c.c.) will increase the conductivity by approximately 15 per cent. A blood loss of 100 cubic centimeters would then be indicated as a loss of 110 cubic centimeters resulting in a slight overtransfusion. This overtransfusion would cease as soon as the hemoglobin had been restored to normal values (Fig. 4). The extent of the overtransfusion is not sufficient to produce circulatory overloading even in cardiac patients. Should overtransfusion and polycythemia result the blood loss would be indicated as being slightly less than the actual amount until the normal state had been restored. Minor deviations in hemoglobin values do not influence conductivity values as can be seen in Table I.

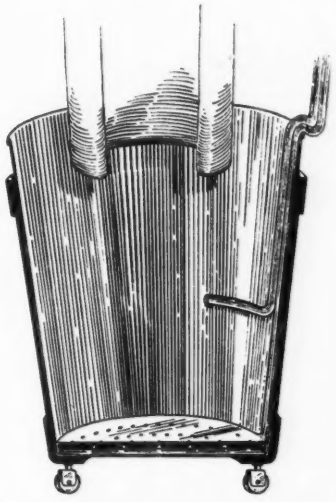


FIG. 5. A disc shaped insert is shown in a kick-bucket. Fluid from the reservoir washes blood into disc from whence it is aspirated into the blood loss meter. This is useful in obstetric applications.

The conductivity method is internally compensated to prevent error by homing on a normal hemoglobin range. No other method possesses this advantage; and, in the hemoglobin and specific gravity methods, anemia induces a deviation away from a normal hemoglobin and toward further error.

The ease and accuracy of measurement with the automatic blood loss meter surpasses both the hemoglobin and the gravimetric methods. The meter is accurate to one-half of 1 per cent. The applications of this apparatus in surgery are

evident. In addition, a great need exists for the accurate and immediate measurement of obstetric blood loss which can easily be accomplished by placing a washout and suction devise (Fig. 5) into the kick-bucket pail into which the Kelly pad drains. The blood loss meter has been recently adapted to pediatric use by adding a new ultrasensitive scale which measures in increments of 10 cubic centimeters up to 800 cubic centimeters for the full scale. With this scale, an addition of 1 cubic centimeter will produce a noticeable deflection on the scale. With this new modification, 1 meter can be used for general surgical operations, pediatrics, and obstetrics.

The blood loss meter assures the surgeon that blood replacement will be adequate. He, himself, is kept in constant contact with the magnitude of hemorrhage by merely glancing at a dial. He is able to make estimates of future requirements from the knowledge of what has already been lost.

The blood loss meter has now been used in more than 50 different thoracic, abdominal, and vascular procedures with blood losses ranging up to 7,500 cubic centimeters. Observations on these cases will be the subject of a separate publication. However, changes in hemodynamics did not occur if a blood deficit as indicated by the meter was not allowed to develop. Replacement could be kept at an even rate and the necessity to pump blood never arose. The practice of pumping blood is not without danger. Serious electrolyte disturbances can and do occur. Ionizable calcium is always absent in citrated blood. If the blood is old, the serum potassium may be high. An elevation of serum potassium coupled with the absence of ionizable calcium evokes grave disturbances in cardiac function and may occasionally lead to cardiac arrest. High blood citrate and ammonia levels may also develop after the rapid transfusion of blood. The hazards of blood replacement are minimized by an even infusion rate which parallels the rate of loss.

SUMMARY AND CONCLUSIONS

An accurate, simplified, practical method for the determination of blood loss has been presented. A machine is described for the measurement of blood loss. It consists of a water filled tub containing an agitator which extracts the electrolytes from the blood sponges and clots. A conductivity bridge measures changes in conductance. A servomechanism continuously brings the bridge into null balance. Automatic temperature compensation is also provided. This machine has been used in the operating room in patients undergoing a variety of operations and those in whom excessive blood loss is contemplated.

REFERENCES

1. Baronofsky, I. D., Treloar, A. E., and Wangensteen, O. H. Blood loss in operations; a statistical comparison of losses as determined by the gravimetric and colorimetric methods. Surgery, 1946, 20: 761.
2. Gram, H. C. Composition and physical properties of normal human blood; a compilation of values from the literature. Am. J. M. Sc., 1924, 168: 511.
3. Habif, D. V. Unpublished data, personal communication to author.
4. Leiter, L., Weston, R. E., and Grossman, J. The low salt syndrome; its origins and varieties. Bull. N. York Acad. M., 1953, 29: 833.
5. LeVeen, H. H. Analysis of micro quantities of sweat for sodium chloride by conductivity method. Proc. Soc. Exp. Biol., N. Y., 1955, 90: 535.

The Book Shelf

THE FIFTH COLUMN AT THE BATTLE OF GETTYSBURG

RUDOLPH MARX, M.D., F.A.C.S., Los Angeles, California

UP TO THE BEGINNING of the twentieth century losses from disease in most wars far outnumbered battle casualties. Various forms of painful infectious diarrhea, commonly called dysentery, have accompanied all armies as a fifth column, and have often decided the outcome of wars.

According to the Greek historian, Herodotus, the army of Xerxes I, King of the Persians in 480 B.C. was seized by plague and dysentery on its retreat from the battle of Salamis, and a great part of it destroyed. This catastrophe facilitated the crucial victory of the Greeks over the remainder of the Persian army left under the leadership of Mardonius in the following year at the battle of Plataea.

The failure of the Crusades was not brought about so much by the scimitars of the Saracens as by the toxins of hostile bacteria of dysentery and other epidemics. In 1227 A.D. dysentery turned back the army of Emperor Frederick II of Germany as he was crossing the Mediterranean on the way to Palestine. The same disease killed St. Louis of France in 1270 A.D., cutting short his second campaign to reach the Holy Land.

One of the decisive battles of history, the Battle of Valmy in 1792 between the French Revolutionary Army and the Royal Prussian Army, was won by dysentery when it attacked the Prussians, forced them to retreat, and saved the French Revolution at its birth.

Many similar examples in the medical history of wars could be added, and they reveal the peculiar phenomenon that dysentery usually plagued more the armies invading another country than it did the soldiers defending their homeland. Several explanations can be offered; one is that an invading army frequently has greater difficulties in maintaining a regular and adequate food supply. When an army has to live from the land, the supply of food is uncertain and often irregular. The invading soldiers frequently experience feast alternating with famine, and eat foods to which they are not accustomed. These factors can contribute to gastrointestinal upsets, weakening the natural defense against the overgrowth of harmful bacteria.

Another consideration is that just as different geographic areas have different flora and fauna, so each soil breeds different crops of bacteria and viruses. The food and water of every region has its own chemical peculiarities and contains different types of microorganisms. The longer a person lives in a certain locality, the more he becomes accustomed to the water of the region and becomes immunized to the specific mixture of the local microbes and viruses that are ever-present in the food, water, and air of his environment, and which even the most modern methods of sanitation cannot eradicate completely. The same minute forms of life which are usually innocuous to the resident are likely to be disease-producing in a newcomer entering from another bacterial milieu. These factors were more potent in former times before the advent of modern medicine and the knowledge of better purification and preservation of food and drink.

Diarrhea was so common in wars that it became the accepted belief that this condition was induced by fear of battle. In a number of realistic novels, scenes are described in which

soldiers, when pinned down by enemy fire, soiled their pants. Medical experience has shown that in most men it was not the emotion of fear, but rather the sickness of dysentery, that produced these unfortunate accidents. The deathly paleness of the victims was more often caused by abdominal cramps and the weakening effects of dysentery than by fright. Modern army doctors have noted that under conditions of regular food supply and the absence of contagious dysentery, cases of diarrhea are the exception among soldiers during battle. Contrary to the popular notion, tension, anxiety, and fear will loosen the bowels only in a few men. In the majority, these emotional states will tend to "tighten them up" and cause constipation. The diarrheas of battles and of wars were usually produced not by fright but by bacteria.

During the American Civil War diarrhea and dysentery led all other diseases in the medical records of the United States Army. More than 25 per cent of all sickness reports were listed under this diagnosis. There were 1,739,135 recorded cases of acute and chronic diarrhea and dysentery, with 44,558 deaths among 2,780,000 Federal soldiers. As great as the occurrence rate of this disease was in the Federal Army, it was almost twice as high among the Confederate troops. According to available medical statistics compiled from comparative periods prior to July 1863, the annual number of cases of diarrhea and dysentery averaged 987 per 1,000 (many had repeated attacks) in the Confederate Army, compared with 543 per 1,000 in the Union Army. Such a high percentage of disablement weakened the effectiveness of the Confederate Army much more compared with that of the Federal Army, since the Confederate Army was only half as numerous.

Most of the cases of dysentery occurred during the summer and fall months. There are indications that General Lee's troops suffered severely from dysenteric disorders in the early summer of 1863 during the Gettysburg campaign. The Confederate soldiers had been weakened by a bleak winter and a hungry spring spent in war ravaged northern Virginia. In April of that year, only 2 weeks before the battle of Chancellorsville, Lee complained to James A. Seddon, Secretary of War for the Confederacy, that the ration of his soldiers "consists of ¼ lb. of bacon, 18 oz. of flour, 10 lbs. of rice, to each 100 men about every third day, with some few peas, and a small amount of dried fruit occasionally as they can be obtained. This may give existence to the troops while idle but will certainly cause them to break down when called upon for exertion."

Such a diet was extremely short on calories and protein. Moreover, it was highly deficient in vitamins. Almost completely lacking was vitamin C, contained in fresh fruits and vegetables. This deficiency led to sporadic occurrences of scurvy among the army of northern Virginia, characterized in its classical form by spongy, bleeding gums, and internal hemorrhages. The more common, milder manifestations of vitamin C deficiency were mostly overlooked since they come on gradually and consist of vague symptoms such as fatigue, weakness, pain in the limbs, mental depression, and decreased resistance against infection.

Before the discovery of the vitamins a great part of the population of the temperate zone was suffering periodically from a certain degree of vitamin C deficiency. In the early spring of each year there was a critical period when the fruits and vegetables stored from the previous season were largely used up and the earliest edible green plants had not yet appeared. It has been assumed that the vague and euphemistic term, "spring fever" originated from the observation of this indisposition recurring each spring, a condition which in reality was caused by vitamin C deficiency.

At the time of the Civil War it was known empirically that fresh vegetables and fruits would cure the symptoms of scurvy. Therefore, at the first signs of spring, Confederate soldiers were sent out into the woods to collect sassafras buds, onions, and other wild vegetation.

The costly Confederate victory of Chancellorsville, 2 months before Gettysburg, was barren of strategic results and did not materially change the dismal picture of poor food supply of the army of Lee. According to Douglas S. Freeman, "of all the arguments that weighed with him" (Lee) in favor of the plan to invade Pennsylvania, "the most decisive single one was that he could no longer feed his army on the Rappahannock. He had to invade the North for provisions regardless of all else." He had to seek food for his undernourished soldiers and fodder for his lean horses in the rich valleys of Pennsylvania, untouched by the war.

Their resistance lowered by months of malnutrition and lack of vitamins, the hungry sol-

diers of the South poured into the well stocked villages of Pennsylvania and gorged themselves with food and drink. They spoiled their stomachs, unaccustomed to such rich fare, and made their weakened gastrointestinal tracts readily susceptible to infection from the ever-present germs that cause dysentery.

An eyewitness account exists of a young officer named John Dooley who commanded the rear guard of Pickett's division on its approach to Gettysburg. He complains of his odious and difficult task of rounding up the numerous stragglers and sending them back to their companies. "For frequently it happens," he wrote, "that many soldiers leave their ranks through necessity, and weakened by diarrhea, can scarcely with all their efforts regain their ranks."

Freeman reports that fully 5,000 "sulkers and sick" contrived to march with the ambulance train from the battlefield of Gettysburg. This number would have represented approximately 10 per cent of Lee's army which was left to retreat. It is likely that a great number of these "sulkers and sick" were suffering from dysentery. A still greater percentage of the army probably suffered from milder forms of this highly contagious ailment, not sick enough to be excused from active duty during the emergency of a critical campaign, but weakened and discouraged by abdominal cramps and diarrhea, and their efficiency as officers and soldiers greatly impaired.

If the invasion of Pennsylvania was motivated by lack of food, the desperate need of shoes for the Confederate soldiers, often marching on gaping soles or on bare, bleeding feet, brought on the Battle of Gettysburg. Napoleon asserted that it needed as slight a provocation as a dog-fight to touch off a battle between two hostile armies poised for action. It is well known that the search for shoes caused a Confederate division to collide with Federal cavalry at Gettysburg—and the battle for the shoes was on—expanding into the decisive Battle of Gettysburg, a battle which had not been planned on this location by either command.

History books discuss the question of the high strategy of the generals and their mistakes, and praise the heroism of the soldiers on both sides. They fail to mention the unromantic factor of comparative medical statistics which gave the North the edge. The army of Mead had a far superior medical service, a better system of sanitation, and was in much better physical condition than Lee's army. Mead fought on interior lines, assuring a regular food supply consisting of meat, bread, and dehydrated vegetables. During July 1863, the army of the Potomac was less affected by dysentery than the army of northern Virginia.

Except for its one defeat at Antietam, Lee's army had won all previous major battles in spite of inferior numbers. It had made up for this deficiency by its superior mobility, greater offensive spirit, and superior leadership. It was a different story at Gettysburg when for once the Confederate Army started the battle with the added advantage of numerical superiority which it maintained until the late afternoon of the second day.

On the afternoon of the first day two Confederate corps attacked and overpowered an outnumbered contingent of Federal troops defending the town of Gettysburg, and took the town. A. P. Hill, commander of the victorious third corps who participated in this victory, was described as sick and very pale on this day. This could explain his apathy and failure to reorganize his troops for immediate pursuit of the Federal columns that were fleeing in disorder toward the key position of Cemetery Hill.

On the second day of the battle it took two divisions of Longstreet's corps, only a few miles distant, the greater part of the day to get in position for attack, giving Mead time to bring up his reserves, reinforce, and extend his line. In spite of this delay Wright's brigade succeeded late in the afternoon, following a desperate struggle, to break through the Federal main position east of the Emmittsburg Road. The battle would have been won if the attack had been supported by the adjoining brigades and co-ordinated with simultaneous attacks of the other corps. There was no such co-ordination of effort on this occasion, nor all during the Battle of Gettysburg. Posey's brigade next to the successful break-through gave only half-hearted support. Mahoney's brigade in close proximity stood idly by. Mead was able to bring up his reserves, force back the victorious troops, and close the dangerous gap. In the twilight of the same day Early took important Federal positions on Cemetery Hill but was compelled to evacuate them for lack of support from Rode's division at his right.

It is an unanswered question how much the

weakening and demoralizing effect of dysentery might have contributed to the strange apathy displayed by officers and soldiers of the Confederate Army at such crucial points of the battle, and to the unaccountable hesitancy and lack of resolution of some of the commanders which caused fatal delays and allowed the chance for victory to slip away.

It appeared to some observers, and later critics, that Lee himself did not show during the Battle of Gettysburg his usual energy, generalship, and good judgment which he exhibited in previous and in later battles. An eyewitness account of W. W. Blackford, officer on the staff of Jeb Stuart, claims that the commanding general was seriously handicapped in his conduct of the battle by an attack of severe diarrhea. In his memoirs, *War Years with Jeb Stuart*, Colonel W. W. Blackford described his experience as follows:

> In the supreme hour of battle the Commander in Chief is the soul of an army, that is, if he is worthy of the army he commands. This being so, anything which affects his physical condition at that time must have a powerful influence upon events. We all know the desperately weakening power of severe diarrhea, and this General Lee had, as I know. When Stuart arrived upon the left flank on the morning of the 2nd (July), there followed several cavalry combats, and during the evening I was sent to General Lee to report what had happened. I found General Lee at his headquarters near the town, but he was in his tent and I was told by one of his staff that I could not see him; so I gave my report to this officer, either Venable or Taylor, I think it was, who took it in to General Lee, and then I sat half an hour with them telling of our expedition. When coming on errands of this kind before, I had usually given my report to General Lee in person, but on this occasion I supposed he was too busy to see me. I was a little surprised to see him come out of his tent hurriedly and go to the rear several times while I was there, and he walked so much as if he was weak and in pain that I asked one of the gentlemen present what was the matter with him, and he told me General Lee was suffering a good deal from an attack of diarrhea. This was the evening of the 2nd day's fight and the day before the final contest. Now who in such a condition would not be affected in vigor of both mind and body, and will not this account for several things which were behind time, or not pushed forward as they should have been the 3rd of July?

Douglas S. Freeman in his introduction to Blackford's memoirs, which he calls an "honest narrative," attempts to refute the contention that General Lee was sick during the Battle of Gettysburg, and states that no officer of Lee's own staff ever reported any illness of the General during the Gettysburg campaign. He challenges the trustworthiness of Blackford's account of such a fateful incident. From the viewpoint of a medical historian it is hard to understand how an intelligent man like Colonel Blackford, a responsible officer on the staff of Jeb Stuart, could have invented the vivid details surrounding Lee's sickness, which Blackford claims to have witnessed under the striking circumstances of a great battle, circumstances that would have made unforgettable the images which the memory received.

The possible explanation of this contradiction could be that diarrhea was so common in the Confederate Army at Gettysburg that it was not thought worth mentioning unless the victim was put completely out of action. The close associates of General Lee may have tended to ignore the embarrassing predicament of their idolized chief, more so as they unconsciously resented so unheroic a situation, and they tried to forget it.

Reviews of New Books

THE INTERESTING and well written account by Samuel James Crowe[1] of the beginnings of the Johns Hopkins Hospital, of Halsted's part in its development, and of some of the men who helped to bring it fame is in a sense the story of the beginning and development of modern surgery in America.

It has been told before but it is recounted here from a new and different viewpoint, and will be read and appreciated by surgeons young and old, and particularly by those who have looked to Johns Hopkins as a leader and as the embodiment of progress and scientific achievement in American medicine.

This is not only the story of Halsted but in varying degrees of Cushing, Dandy, Mitchell, Hugh Young, Baer, Baetjer, and of the author, Crowe; and of their association with the chief actor in the drama.

One cannot help but regret that the author could not have lived to see the publication of his beautifully written volume. He died November 15, 1955 at the age of 72 years. —*Sumner L. Koch.*

THE QUALIFICATIONS of Esther Pohl Lovejoy for the authorship of the volume *Women Doctors of the World*[2] are manifold: a long and active life, a great deal of information about women doctors, and a wide contact with the world. As Chairman of the American Women's Hospitals Committee of the American Medical Women's Association she was, and still is, in a position to hear a great deal about the careers and accomplishments of medical women, more particularly in their organized activities. The result is a little volume of notes dealing chiefly with those doctors who were pioneers in the emergence of women into the world of medicine. Since the pioneers were rather constantly occupied with doors which either remained closed before them or, as in the case of the University of Edinburgh, slammed resoundingly while the students were in the midst of their studies, the theme of doors is perforce a major one in the narrative; but the author sails through with spirit and without rancor; and the means by which the doors were finally caused to bulge or sag were often diverting and sometimes inspiring. Certainly most spectacular among the pioneers was Dr. James Barry who "seems to have been born in 1812 of the University of Edinburgh—to have sprung full-armed with a diploma from that womb of learning into the military medical world." Doctor Barry dealt with closed doors by impersonating a man and then sustained the impersonation through a distinguished career in the British Army Medical Services, finally as staff surgeon of the garrison at Cape Town, and the Governor's medical advisor.

"Prompt to resent offense and a good shot, Doctor Barry seems to have favored duels with pistols, and this temper tended to discourage unseemly reference to her dainty person and beardless chin. Her unmanly appearance created gossip, but her courage, skill and devotion to duty commanded respect."

Notwithstanding the affair of the doors, it is apparent that the pioneers had not only enemies but friends—distinguished ones. In this smaller group could be cited the Earl of Shaftesbury, Charles Darwin, Professor Thomas H. Huxley, the Dowager Lady Stanley of Alderly, Sir James Stansfeld, M.P., and the Right Honorable W. Cowper-Temple, M.P.—members of the board of governors of the London School of Medicine for Women opened in October 1874. In the United States the four great Baltimore leaders, Halsted, Kelly, Osler, and Welch might justly be included, and in Russia the coffin of Alexander Borodin bore a silver crown with the inscription:

"To the founder, protector and defender of the School of Medicine for Women; to the supporter and friend of students."

So Doctor Lovejoy's chronicle, rambling and unpretentious as is its presentation, contains many curious data and furnishes a very readable addition to the story of the development of modern medicine.

—*Edith B. Farnsworth.*

THE TREATISE on hypospadias and its treatment by Hans Serfling[3] of the University of Halle, Germany, contains 344 pages and is encyclopedic in its scope.

The treatment of hypospadias has long been a frustrating experience to most surgeons. The poor results, due to fistula formation, postoperative stricture, and sloughing of the area operated upon, requiring multiple stage operations until a satisfactory or even passable result was obtained, have been a trying ordeal for the patient, his parents, and the surgeon.

Some of the older techniques have given brilliant results in the hands of a few specially qualified operators who had an interest in the subject and possessed an aptitude for plastic surgical routines. With the elaboration of some of the newer techniques (notably that of Dennis-Browne) and as a result of the stressing of certain well established fundamental principles by Blair, Davis, Culp, Cecil, Nesbit, and many others, the incidence of failures is rapidly decreasing and it is now becoming possible for the average competent urologist or plastic surgeon to achieve excellent end results.

The appearance of this well written volume is, therefore, timely. The author, stimulated by a long, practical experience with the operative correction of cases of hypospadias at the Surgical Clinic of the

[1]HALSTED OF JOHNS HOPKINS; THE MAN AND HIS MEN. By Samuel James Crowe, M.D., 247 pages, illustrated. $5.00 Springfield, Ill.: Charles C Thomas, 1957.

[2]WOMEN DOCTORS OF THE WORLD. By Esther Pohl Lovejoy, M.D., LL.D., D.Ph.(Hon.). 413 pages, 50 illustrations. $5.95. New York: The Macmillan Co., 1957.

[3]DIE HYPOSPADIE UND IHRE BEHANDLUNG. By Dr. med. Hans Joachim Serfling. 344 pages, 338 illustrations. DM 53.50. Leipzig: Georg Thieme, 1956.

University of Halle, has presented his subject in a truly scholarly, but practical, fashion. The anatomy, embryology, teratology, diagnosis, differential diagnosis, endocrinologic aspects, and surgical treatment are discussed in exhaustive detail. Practically every known surgical procedure is presented and illustrated by excellent stage drawings. The discussion of the merits and shortcomings of these various procedures is presented with a sound, practical, and common sense approach; fundamental principles are constantly stressed. The review of the world literature is exhaustive, as demonstrated by approximately 600 references which are repeatedly discussed in the text.

This scholarly volume is written in a pleasant style which makes for easy reading. It is well printed with easily legible type upon an excellent grade of glossy paper. The 338 illustrations are superb. It is an excellent reference work for those interested in the treatment of hypospadias. —*Frederick A. Lloyd.*

THE BOOK by Brocher[4] is a monograph on the prognosis of diseases of the vertebral column. For a period of 25 years Professor Brocher has made a study of the pathology of the spinal column. He has previously published monographs on related subjects—"The Displacement of Vertebrae in the Lumbar Area" and "Tuberculosis of the Vertebrae and its Differential Diagnosis."

The purpose of this study is to aid in preventing the occurrence of disturbances of the back due to occupation. The primary concern (in the treatment of back conditions) is establishment of the functional capacity of the back, particularly in relationship to occupation. This is significant, not only for the patient, but also has social and economic significance.

For anyone who is interested in diseases of the back there is much of importance in this monograph to justify a summary of the essential facts.

The spinal column acts as a protection of the internal organs and makes for erect posture of the body. The back acts as a static support. At the same time, it can be a structure with much movement. Another function of the spine is to act as an elastic spring to absorb shock.

Loss of function in the spine may result in a decrease in economic position for the individual. The most important time to establish the prognosis of the vertebral column is between the ages of 15 to 25 years.

The spine is examined with the patient standing. The patient is examined in the relaxed position as well as with maximum correction. The dorsal and lumbar spine are examined for the presence of increased curvatures. A flat back means that there is a loss of elasticity in the back and that there is a predisposition to pain. The type of increased curve is examined: the rounded dorsal indicative of Scheuermann's; the sharp angulation suggestive of tuberculous destruction; the right dorsal and left lumbar lateral curvature typical of idiopathic scoliosis; the loss of movement indicative of spondylitis deformans. The presence of spina bifida is suggested by the absence of the spinous processes. The increased angulation with a sharp angle at the lumbosacral articulation and the short trunk is diagnostic of spondylolisthesis. Essential to the examination are roentgen studies. These are preferably taken standing; full length x-rays are not limited to the chiropractors.

A thorough review is made of Scheuermann's diseases and shows early and late stages and cases in which the bone breaks through the cartilage to form Schmorl's bodies. Some cases have very marked changes in a small area with severe kyphosis, others have mild changes with gentler kyphoses. The late stages show arthritic changes with loss of disc space at the height of the curve. The most typical changes are in the dorsal area but changes may also occur in the lumbar area. There are also changes in the chest. The pain which occurs in Scheuermann's is due to a decompensation of the back. It is very difficult to establish the functional capacity of a back with Scheuermann's disease from the appearance of the vertebrae alone. Much depends on the strength of the trunk muscles. The prognosis is dependent on more than the amount of curve or amount of bone change. Patients with Scheuermann's disease should avoid occupations which require heavy lifting. This is of importance to the patient as well as to the employer and to the insurer.

The degenerative diseases of the vertebral column are important clinically when moderate or advanced. Slight changes may be assumed to be within the range of normal, depending on the age of the patient. Important clinical signs, as the result of degenerative changes, are low back pain, sciatica, and referred pain in the neck and upper extremities. The hypertrophic overgrowth and loss of intervertebral spaces may cause nerve irritations. The loss of joint space may indicate a herniated nucleus pulposa. Certain occupations, particularly those in which there is much bending and heavy lifting, are conducive to hypertrophic arthritic changes. If these changes are seen in patients between 15 and 25 years of age, they are important in prognosis and in consideration of selection of occupation. Familial tendency exists, and if present must be considered in a choice of occupation.

All structural changes and failures of development of the vertebrae are significant. Fusion of the vertebra or partial formation of the vertebra can give rise to symptoms. Spina bifida occulta may lead to structural weakness. A congenital difference in the two surfaces at the lumbosacral joint may cause weakness in the back. Spondylolisthesis and failure of the various parts of the fifth lumbar vertebra to form may be a serious handicap. On the other hand, a defect can be present and the back may be thoroughly adequate. Sacralization of the fifth lumbar vertebra can excite an irritation and cause pain.

Spondylitis deformans is the most common of the infectious diseases. Various tumors may occur in the spine and be a cause of disability. Results of injury and operation are factors in establishing the amount of function possible for the individual. Many fused spines have been able to carry out their normal work; others have not. It is impossible at the present time to establish the exact amount of disability that will result from the morphologic changes as seen in the

[4]DIE PROGNOSE DER WIRBELSAEULENLEIDEN; EINE BERUFSPROPHYLAKTISCHE BETRACHTUNG. By Prof. Dr. J. E. W. Brocher 67 pages, 33 illustrations. 12.80 DM. Stuttgart: Georg Thieme, 1957.

roentgenogram. The entire individual must be considered in trying to establish the functional capacity of a vertebral column. Much can be done by means of routine investigation of the back, including roentgenologic studies, to establish the possibility of an increased risk for the individual to do heavy work.

These studies should be further pursued since they are of great importance socially and economically; they are of concern to industry, insurance companies, and to the individual.

The book has excellent reproductions of roentgenograms that illustrate the subject matter clearly.

—*Emil D. W. Hauser.*

THE VOLUME by Ronald Furlong[5] presents in very readable and clearly stated fashion the current teaching and practice of the Orthopedic Department of St. Thomas Hospital, London. It deals essentially with the care of the acute injury and acute infection as they are met with by the surgeon in his practice. No attempt is made to describe complicated reconstructive procedures and a restrained attitude is evidenced throughout the volume in case of insufficiently established techniques. The volume is sound throughout and represents present day British practice. It abounds in many practical suggestions, often most intriguingly stated. The present concept of wound care is based on respect for tissues; the soil is more important than the seed. "Absence of septic inflammation after surgery is explained not by absence of organisms in the wound but by avoidance of haematoma and especially avoidance of tissue damage during the course of the operation."

In the discussion of technique the various incisions are described and among them the Henry incision for exposure of the ulnar side of the palm. The whole ulnar half of the palm is raised from an incision which passes from the midlateral side of the little finger upward along the ulnar border of the hypothenar eminence to the wrist. The pisiform bone and flexor carpi ulnaris may be lifted forward to give more adequate exposure.

Furlong advises against removal of the tourniquet or rather deflation of the blood pressure cuff at any time before application of the final dressing. This practice may permit some oxygenation of the tissues and will permit the surgeon to "satisfy himself that no major bleeding continues." He states that after reinflating the cuff congestion, swelling, and oozing persist. This procedure differs from the practice in many clinics where it is routine to deflate the cuff following the initial preparation of the operative field, to control bleeders and then to reinflate the cuff, complete the operation and wound closure, and apply the compression dressing before final deflation.

Furlong has supplied a long felt need for the proper name for a compression or pressure dressing. He calls it a *contour* dressing which avoids the interpretation of a tight pressure dressing so frequently applied by the novice.

The methods of tendon repair described are essentially those outlined by Bunnell. Furlong advocates in selected cases a tenolysis with the use of areolar tissue from the forearm as a blanket to wrap about the freed tendon. The procedure is of value only when adhesions are of limited extent. The indications and technique of free tendon grafting follow essentially the recognized techniques.

Except for the digital nerves primary nerve suture is not advised. This is in accord with the conclusions reached by Seddon and his collaborators, and as Furlong states "the bulk of peripheral surgical nerve knowledge is based on experience with gunshot wounding or at least blunt injury." His point of view is not whole-heartedly shared by American surgeons although it must be conceded that nerve repair demands skill and experience not everywhere available and, as Furlong states, "If . . . the word goes out that delayed suture is desirable, the delay of several weeks will permit the patient to be transferred . . . to a Peripheral Nerve Unit where the necessary experience is available."

Primary closure of all open injuries is strongly advocated, and the usual methods of securing this, where skin is lacking, are described. Elective amputation of digits follows simple, commonsense indications. A useless finger need not be amputated unless it hampers function. No viable portion of the thumb should be removed, but almost anyone can spare one finger if the others are normal. Where many fingers are damaged, however, the maximum length of each should be preserved. The author seems to be rather lukewarm toward thumb reconstruction.

Infections of the hand are described briefly but adequately. Whether the present more benign course of infections can be attributed so largely to the antibiotics, I think is open to question. Furlong recognizes this also when he notes that ignorance and neglect are likewise important. Excision of localized inflammation, apparently widely practiced in Great Briatin, seems to many of us hazardous and one gains the impression that it has only limited application.

The chapter on tendon repair comprises about one-third of the volume and follows established practices. Furlong has not entirely given up primary suture in "no man's land," and one gains the feeling that he advocates it for those situations in which proper experience and facilities are available. He distinguishes between delayed primary suture and secondary suture. Delayed primary suture is undertaken before the divided tendons have become adherent (usually not over 3 to 4 weeks after injury) and has the same prognosis as primary repair. Secondary suture on the other hand is undertaken later, and by that time adhesions have developed and provision must be made to secure a gliding tendon, usually by areolar tissue transplant.

Fractures are dealt with in a very practical fashion, emphasis being placed on functional restoration rather than strict anatomic reduction. This applies particularly to the metacarpal and digital fractures. He states, for example, in connection with Bennett's fracture that "some surgeons feel it better to make no attempt to reduce the fracture." Treatment by early active and passive motion is more likely to lead to a functionally normal thumb, despite the abnormal appearance, than the more usual methods of immobilization.

Furlong devotes a number of paragraphs to a phenomenon which it is certain most of us have seen but

[5] INJURIES TO THE HAND. By Ronald Furlong, F.R.C.S. 215 pages, 99 illustrations. $9.00. Boston: Little, Brown & Co., 1957.

have not recognized. Following division of the flexor tendons to a digit the patient loses ability to flex that digit actively and if the situation persists long enough the pattern of the original motion is lost. Flexion of the finger is possible at the metacarpophalangeal joint by the interossei which also extend the interphalangeal joints. At times after tendon repair the same tendency to flex the metacarpophalangeal and extend the interphalangeal joints persists and effort must be made to break the new pattern. Furlong speaks of this as *intrinsic dominance*. If it cannot be broken by physical therapy and exercises it may require repeated ulnar nerve block.

While there are minor points in which agreement is not unanimous one can find little of major significance with which to take exception. One point, however, which I should like to clarify is that the Chicago school does not immobilize tendons for 5 weeks after repair.

I cannot refrain from citing a few quotations from the book since they indicate a break from the usually dry presentation of surgical topics and would only come from a teacher who impresses a point by colorful illustrations. The book is full of them but a few will suffice to make the point. In discussing the anatomy of the hand: "Individual action of the extensor proprius indicis is noted in the conventionalized sign indicating the 'way-out' and that of the extensor quinti digiti in the extended little finger of the genteel bar maid pouring bottled beer." "The recognition of a carpal bone by palpation in the pocket advertises a high level of tactile sense but little else." He notes that the proximal and distal row of the carpal bones are joined by the scaphoid "like the apex of a wish bone." In the caption of an illustration of a finger which had been burned by hot applications Furlong notes, "In this instance the patient used a lot of heat and no intelligence." In discussing the length of sublimis tendon to be left subtending the proximal interphalangeal joint, "The happy medium is found by good luck rather than good judgement." On speaking of rupture of the extensor pollicis longus, "The drummer boy marches along beating his kettle drum with martial vigor when suddenly, to his lasting shame, one of the drum sticks flies out of his hand," and finally in discussing dislocation of the distal interphalangeal joints as they occur in cricketers: "In nearly all instances they are wise enough to keep away from doctors and as a result they furnish themselves with knobbly deformed terminal joints which are mobile and controlled and painless."

Finally, one should comment on the excellently reproduced photographs and roentgenograms, each of which is most suitable and to the point.

It is not possible to discuss extensively all the material in this excellent volume. It is a dependable guide for anyone who has to deal with these conditions and can be heartily recommended.—*Michael L. Mason.*

VOLUME III of Rob and Smith's *Operative Surgery*[6] covers the rectum, anus, and thorax and has a list of master contributors as distinguished as the two previous volumes. The written text for each operation or diagnostic procedure states precisely the indications, special contraindications, preoperative preparation, anesthesia, postoperative care, and any special complications to be looked for, while the surgery itself is profusely illustrated to make the whole procedure a simple step-by-step operation. There is so much that is excellent it is difficult to comment upon any one special subject. The methods used are British, but they are generally not fundamentally different from the recommended treatment in this country, consequently the volumes are immensely valuable as teaching manuals any place in the world.

The surgeons and others contributing to these volumes are among the top men in their country and are masters of their craft. Their affiliations, mainly with London hospitals, have been mentioned, since it gives the reader the names of many of the great medical institutions in Britain.

American surgeons will be pleased at seeing Lockhart-Mummery of St. Mark's fame describe and beautifully illustrate the management of hemorrhoids, fissure-in-ano, and ischiorectal abscess. Anorectal atresia with associated fistulas is handled superbly by J. J. Mason Brown, Surgeon in Charge of the Royal Edinburgh Hospital for Sick Children. Mr. C. Patrick Sames, Surgeon to the Royal United Hospitals, Bath, gives credit to Miles for the use of rectosigmoidectomy for complete rectal prolapse. Swenson's (of Boston) method of rectosigmoidectomy for treating Hirschsprung's disease is well presented by J. C. Goligher, Professor of Surgery at Leeds, who also illustrates methods for resections of the rectum for cancer with restoration of colon continuity. Lloyd-Davies of Middlesex and St. Mark's Hospitals beautifully depicts the combined excision of the rectum by the three established methods: the abdominoperineal (Miles), perineo-abdominal (Grey Turner and Gabriel), and the synchronous employment of both. Excision of pilonidal sinus is presented by K. W. Wilkinson of St. George's Hospital.

The section on the thorax is again a masterpiece by experts who describe and profusely illustrate the various steps of their most common procedures. Kenneth Price of my wartime Frenchay Hospital, Bristol, discusses bronchoscopy, esophagoscopy, thoracoscopy, and division of adhesions. L. L. Bromley of St. Mary's Hospital covers aspiration of the pleural and pericardial cavities, induction of artificial pneumothorax, bronchography, and phrenic nerve crush. R. H. F. Brain of Guy's presents the fundamentals of the so-called "standard approaches" to the chest in a graphic series of illustrations. Vernon C. Thompson of the London Hospital covers intercostal drainage of empyema. C. E. Drew of Westminster and St. George's Hospitals handles tumors of the chest wall, and W. P. Cleland of the Brompton Chest Hospital and King's College Hospital has the assignment for thoracoplasty with apicolysis, decortication, extrapleural pneumonolysis, and extraperiosteal plombage. A. H. M. Siddons of St. George's describes pneumonectomy, lobectomy, segmental resection of the lung, and removal of cysts.

[6] OPERATIVE SURGERY. Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Vol. III. Rectum and Anus; Thorax. 215 pages, illustrated. Vol. IV. Head and Neck and Clearance of Lymph Nodes, Vascular Surgery, Endocrine Glands. 378 pages, illustrated. London: Butterworth & Co., Ltd., 1957.

In the section on heart surgery Mr. D. G. Melrose of the Postgraduate Medical School, London, describes and illustrates the methods of obtaining ideal conditions for these operations. Ronald Belsey, again of my wartime Frenchay Hospital, Bristol, covers pericardiectomy and drainage of the pericardium; Mr. A. L. d'Abreu, Queen Elizabeth Hospital and Children's Hospital, Birmingham, presents the treatment of persistent ductus arteriosus; T. Holmes Sellors of Middlesex Hospital has the assignment for the tetralogy of Fallot and pulmonary valvotomy; D. N. Ross of Guy's Hospital presents the open and closed methods for atrial septal defects; A. Logan, Lecturer in Thoracic Surgery, University of Edinburgh, does coarctation of the aorta; J. R. Belcher of the London Chest Hospital describes mitral valvotomy and Ivor Lewis, Surgeon to the Welsh Regional Board, presents the management of pulmonary embolectomy, while G. Kent Harrison of St. Thomas's Hospital tells and shows what to do for cardiac arrest.

Operations on the mediastinum are beautifully done and include removal of tumors or cysts and excision of intrathoracic goiter by George A. Mason, Lecturer in Thoracic Surgery, King's College, University of Durham, Newcastle-upon-Tyne, and operations for carcinoma of the esophagus and for achalasia or cardiospasm by R. H. Franklin, Senior Lecturer in Surgery, Postgraduate Medical School of London.

Volume IV of Rob and Smith's *Operative Surgery* covers various aspects of the head, neck lymph nodes, vascular surgery, and endocrine glands. Its contributors are again British master surgeons of long experience.

Mr. K. Owen, Assistant Director of the Surgical Unit of St. Mary's Hospital, covers excision of subcutaneous dermoid cyst, excision of pinna, and excision of osteoma of vault of the skull. Mr. M. R. Ewing, Professor of Surgery at the University of Melbourne, writes on a condition we seldom see in this country, that is, surgical treatment of tuberculous cervical lymph nodes and incision of acute cervical abscess. He also discusses block dissection of cervical lymph nodes with 26 step-by-step beautiful illustrations. Mr. B. McN. Truscott of the United Cambridge Hospitals describes removal of cystic hygroma, removal of submental dermoid cyst, branchial cyst and cervical sinus, carotid body tumor, excision of pharyngeal pouch, tracheostomy, and operation for cervical rib. Carcinoma of the pharynx is well illustrated by Ronald W. Raven of Westminster Hospital. Excision of axillary and inguinal lymph nodes is well done by R. W. Nevin of St. Thomas's Hospital. For a variety of neoplasms in the area John F. Simpson of St. Mary's Hospital presents excision of various parts of the maxilla and mandible. Carcinoma of the mouth and tongue alone and with resection of the mandible and glands of the neck is well described by Ronald W. Raven of Westminster Hospital, who also does epithelioma of the lip and innocent tumors of the tongue and floor of the mouth. Sialography is presented by J. N. Pattinson, radiologist at Middlesex Hospital. Of the same hospital, Mr. David H. Patey covers conservative and radical parotidectomy, enlargement of the parotid duct orifice, drainage of a parotid abscess, intraoral removal of submandibular duct calculus, and excision of submandibular gland. B. W. Fickling, who is Senior Dental Surgeon to a number of London hospitals, describes the removal of both dental cysts and tumors.

The section on vascular surgery is very well done. Charles Rob, one of the General Editors of these volumes and Professor of Surgery at St. Mary's Hospital, and E. G. Tuckwell, Surgeon of St. Bartholomew's Hospital and Dean of St. Bartholomew's Hospital and St. Bartholomew's Hospital Medical School, write on sympathetic ganglion block, on upper thoracic sympathetic ganglionectomy, on lumbodorsal sympathectomy and splanchnicectomy and presacral neurectomy, and on lumbar sympathetic ganglionectomy. Charles Rob alone presents congenital arteriovenous fistulas and the treatment of arterial aneurysms.

Concerning varicose veins and their complications, my friend Josephus C. Luke of McGill University, Montreal, well presents the fundamental treatment by ligation and stripping, F. B. Cockett of St. Thomas's adds the handling of incompetent perforating veins of the leg, and R. P. Jepson, Professor of Surgery at Sheffield, discusses gravitational ulcers and phlebography. He further presents the indications for and technique of deep vein ligation, inferior vena cava ligation, and Achilles tenotomy. Exposure or ligation of major blood vessels is the assignment of H. H. G. Eastcott of St. Mary's Hospital who takes up in order the innominate, subclavian, axillary, brachial, common carotid, internal and external carotid, abdominal aorta, common iliac, external iliac, common femoral, superficial femoral in Hunter's canal, popliteal artery, and posterior tibial artery. He also describes various methods of arterial suture, embolectomy, artery or vein graft, arteriovenous fistulas, and thromboendarterectomy. Arteriography and aortography are described by James Bull, radiologist to St. George's. Excision of subcutaneous tissues, for lymphedema is covered by R. Mowlem, Surgeon in Charge, Plastic Department, Middlesex Hospital and Center for Plastic Surgery, Mount Vernon Hospital, Northwood.

Part 8 on the endocrine glands is an excellent chapter. General Editor Charles Rob discusses subtotal and radical thyroidectomy, hemithyroidectomy, resection enucleation and cervical approach to retrosternal goiter, excision of lingual thyroid, excision of thyroglossal cyst or sinus, and exploration of the parathyroid glands. Thymectomy is handled by George A. Mason of King's College, University of Durham, Newcastle-upon-Tyne, while exposure of the pituitary region by the frontal approach is done by G. K. Tutton, University Lecturer in Neurosurgery, Manchester Royal Infirmary. Mr. W. P. Greening of the Royal Marsden and Charing Cross Hospitals presents the subject of interstitial irradiation of the pituitary. Crossing the Irish Sea, we find J. Seton Pringle, Professor of Surgery, Royal College of Surgeons in Ireland, handling the transdiaphragmatic exposure and resection of the adrenal gland for tumor, subtotal adrenalectomy by the abdominal approach, and total adrenalectomy using lumbar incisions, with a fine text and beautiful illustrations for these relatively recent surgical operations.

Both the surgical resident undergoing his training

and the experienced surgeon will find a great deal of value in these volumes. The concise, carefully written text and the beautiful illustrations by a group of specialists present a mode of treatment the reader should easily translate into a well performed operation. The editors, consultants and associate editors, and contributors should be congratulated on their effort. These volumes should be in every medical school and hospital library, and could profitably be purchased by every general surgeon as a valuable addition to his at-hand references in operative surgery.

—*Walter G. Maddock*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE GLAUCOMAS. By H. Saul Sugar, M.D., F.A.C.S. 2nd ed. 516 pages, illustrated. $13.50. New York: Paul B. Hoeber, Inc., 1957.

SYMPOSIUM ON DISEASES AND SURGERY OF THE LENS. Editor, George M. Haik, M.D., F.A.C.S. Associate Editor, Elizabeth M. McFetridge, M.A. Art Editor, Don Alvarado. 260 pages, illustrated. $10.50. St. Louis: C. V. Mosby Co., 1957.

THE DIAGNOSIS AND TREATMENT OF INFECTIONS. By D. Geraint James, M.D., M.R.C.P. (Lond.). 234 pages, not illustrated. $6.00. Springfield, Ill.: Charles C Thomas, 1957.

CLINICAL NEUROSURGERY; PROCEEDINGS OF THE CONGRESS OF NEUROLOGICAL SURGEONS. Chicago, Illinois, 1956. Vol. IV. 142 pages, illustrated. $7.00. Baltimore: Williams & Wilkins Co., 1957.

ANOMALÍAS MORFOLÓGICAS DE LA PLACENTA Y SU SIGNIFICADO CLÍNICO. By Dr. Oscar Agüero. 107 pages, illustrated. Caracas, Venezuela: Artegrafia, C. A., 1957.

ARTIFICIAL INSEMINATION IN THE HUMAN. By A. M. C. M. Schellen, M.D. Introduction by Sophia J. Kleegman, M.D. 420 pages, not illustrated. $14.00. Houston: Elsevier Press, Inc., 1957.

INCURABLE WOUND. By Berton Rouechë. 177 pages, not illustrated. $3.50. Boston: Little, Brown & Co., 1958.

RHYTHMUSSTOERUNGEN DES HERZENS: SYSTEMATIK-URSACHE UND KLINISCHE BEDEUTUNG THERAPIE. By Konrad Spang. Die Morphologie des Reizleitungssystemes, ihre Orthologie und Pathologie by Prod. Dr. Med. W. Doerr. Physiologie der Herzirregularitäten by Priv. Doz. Dr. W. Trautwein. 659 pages, 228 illustrations. $35.25. Stuttgart: Georg Theime, 1957.

NIERENKRANKHEITEN; PHYSIOLOGIE PATHOPHYSIOLOGIE, KLINIK UND THERAPIE. By Hans Sarre. 540 pages, illustrated. $14.05. Stuttgart: Georg Theime, 1958.

DIE GEBURTSHILFLICHEN OPERATIONEN IHRE AUSFUEHRUNG UND ANWENDUNG. By Prof. Dr. Med. Heinrich Martius. 281 pages, illustrated. $7.05. Stuttgart: Georg Theime, 1958.

MICROSCOPIC ANATOMY OF THE TEMPORAL BONE; A PHOTOGRAPHIC SURVEY OF SERIAL SECTIONS OF THE TEMPORAL BONE CUT IN THE THREE ROUTINE PLANES OF SECTIONING HUMAN SPECIMENS. By Dorothy Wolff, Ph.D., Richard J. Bellucci, M.D., and Andrew A. Eggston, M.D. 414 pages, illustrated. $12.50. Baltimore: Williams & Wilkins Co., 1957.

THE ILLUSTRATED BIRTH CONTROL MANUAL. By Valeria Hopkins Parker, M.D. 392 pages, 178 illustrations. New York: Cadillac Publishing Co., Inc., 1957.

BRAIN TUMORS; THEIR BIOLOGY AND PATHOLOGY. By K. J. Zülch, M.D. American ed. based on the 2nd German ed. Translated by Alan B. Rothballer, M.D., and Jerzy Olszewski, M.D., Ph.D. 308 pages, illustrated. $9.50. New York: Springer Publishing Co., Inc., 1957.

AN INTRODUCTION TO FUNCTIONAL ANATOMY. By David Sinclair, M.D. 426 pages, illustrated. Springfield, Ill.: Charles C Thomas, 1957.

PRINCIPLES OF GYNAECOLOGY. By T. N. A. Jeffcoate M.D., F.R.C.S. (Edin.), F.R.C.O.G. 696 pages, illustrated. $15.00. London: Butterworth & Co., Ltd., 1957.

EDEN & HOLLAND'S MANUAL OF OBSTETRICS. 11th ed. By Alan Brews, M.D., M.R.C.P. (Lond.), F.R.C.S. (Eng.), R.R.C.O.G. 751 pages, 371 illustrations. $11.00. London: J. & A. Churchill, Ltd., 1957.

LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIAL-DIAGNOSTIK. Vol. I. Erkrankungen der Brustorgane. By Prof. Dr. Werner Teschendorf assisted by Prov. Doz. Dr. P. Thurn. 1183 pages, 1138 illustrations. $50.00. Stuttgart: Georg Thieme, 1958.

CLINICAL ORTHOPAEDICS. Vol. X. Editor-in-chief, Anthony F. DePalma. 367 pages, illustrated. $7.50. Philadelphia and Montreal: J. B. Lippincott Co., 1957.

URINE AND THE URINARY SEDIMENT; A PRACTICAL MANUAL AND ATLAS. 2nd ed. By Richard W. Lippman, B.S., M.D. 140 pages, illustrated. $8.50. Springfield, Ill.: Charles C Thomas, 1957.

DER LEHRSTUHL FUER CHIRURGIE AN DER RHEINISCHEN FRIEDRICH WILHELMS-UNIVERSITAET BONN 1818–1953. By Erich Freiherr Von Redwitz. 106 pages, illustrated. Bonn: Bonner Universitaets Buchdruckerei, 1957.

RECENT ADVANCES IN UROLOGY. By Howard G. Hanley, M.D., F.R.C.S. with the assistance of specialist contributors. 270 pages, 83 illustrations. $7.00. Boston: Little, Brown & Co., 1957.

ABNORMAL LABOR. By L. A. Calkins, M.D. 70 pages, not illustrated. $2.75. Springfield, Ill.: Charles C Thomas, 1958.

THE POSTOPERATIVE CHEST; RADIOGRAPHIC CONSIDERATIONS AFTER THORACIC SURGERY. By Hiram T. Langston, M.D., Anton M. Pantone, M.D., and Myron Melamed, M.D. 228 pages, illustrated. $8.00. Springfield, Ill.: Charles C Thomas, 1958.

TEXTBOOK OF GYNECOLOGY. 2nd ed. By John I. Brewer, M.D. 742 pages, illustrated. $15.00. Baltimore: The Williams & Wilkins Co., 1958.

CLINICAL HEART DISEASE. By Samuel A. Levine, M.D., F.A.C.P. 5th ed. 673 pages, 216 illustrations. $9.50. Philadelphia and London: W. B. Saunders Company 1958.

ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Bibliografia—1954. Directed by O. Scaglietti. Edited by L. Gui. Vol. VIII. 233 pages, illustrated. Firenze: Edizione Scientifiche dell "Institito Ortopedico Toscano," 1957.

THE ROOSEVELT HOSPITAL 1871–1957. 358 pages, illustrated. New York: The Roosevelt Hospital, 1957.

THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE; A TEXTBOOK ON PHARMACOLOGY AND THERAPEUTICS FOR MEDICAL STUDENTS, PHYSICIANS, AND THE MEMBERS OF THE PROFESSIONS ALLIED TO MEDICINE. 4th ed. By John C. Krantz, Jr., and C. Jelleff Carr. 1313 pages, illustrated. $14.00. Baltimore: Williams & Wilkins Co., 1958.